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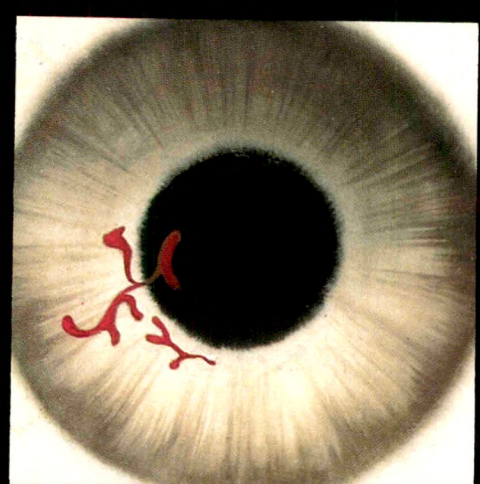
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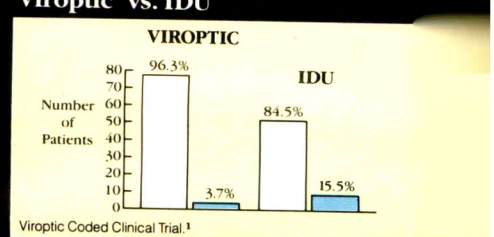
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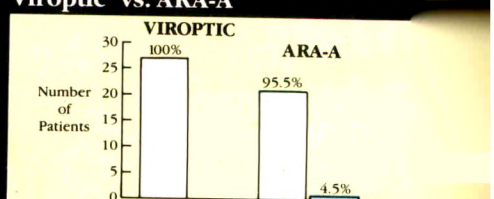
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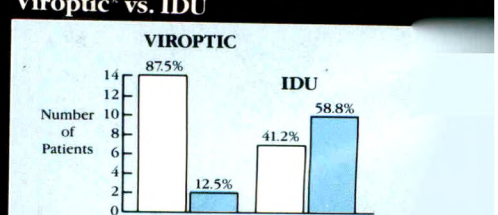
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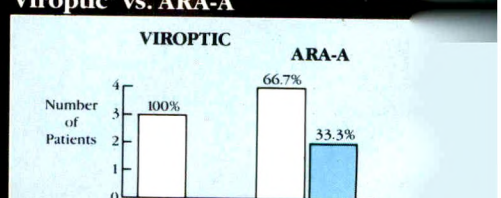
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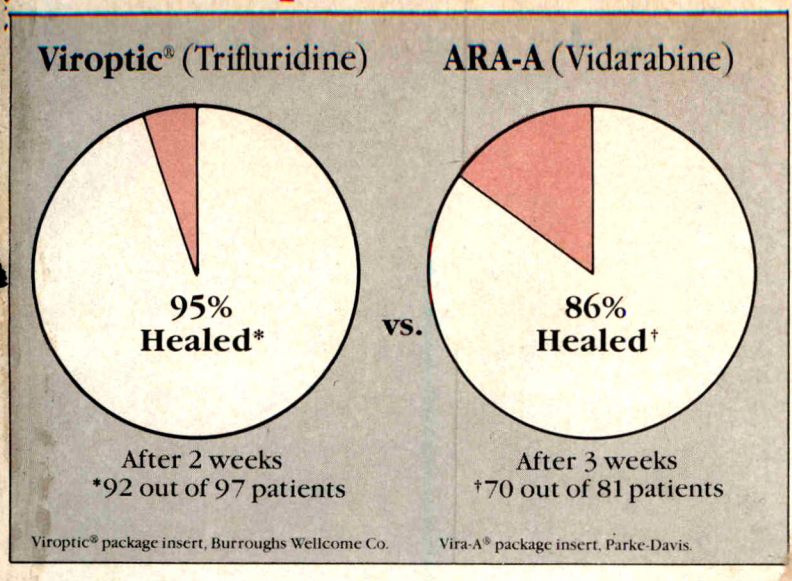
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References

1. Data on file, Medical Division, Burroughs Wellcome Co.
2. McKinnon JR, McGill JI, Jones BR: A coded clinical evaluation of adenine arabinoside and trifluorothymidine in the treatment of ulcerative herpetic keratitis, in Pavan-Langston D, Buchanan RA, Alford CA Jr (eds): *Adenine Arabinoside: An Antiviral Agent*, Raven Press, New York, 1975, p 403.
3. Kaufman HE, Centifanto-Fitzgerald YM, Varnell ED: Herpes simplex keratitis. *Ophthalmology* 1983;90:700-706.

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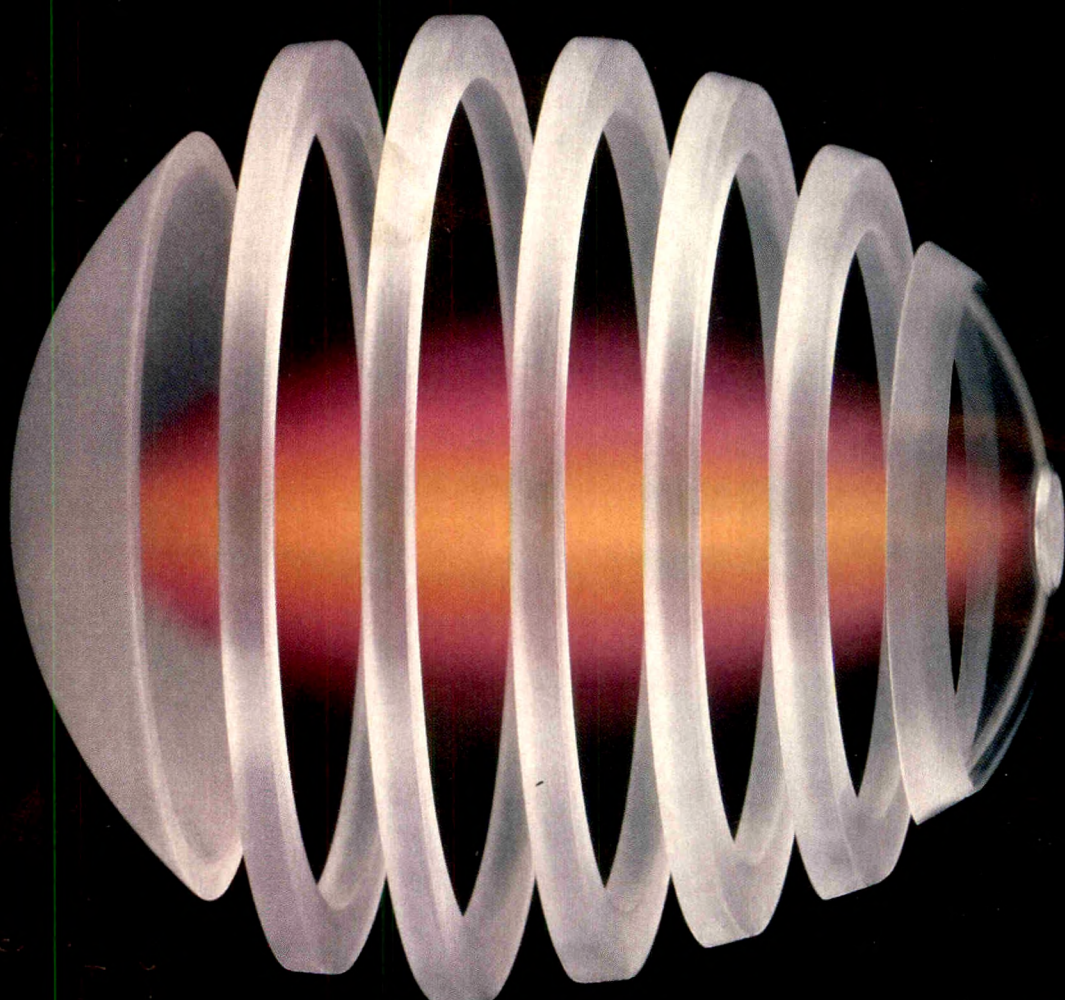
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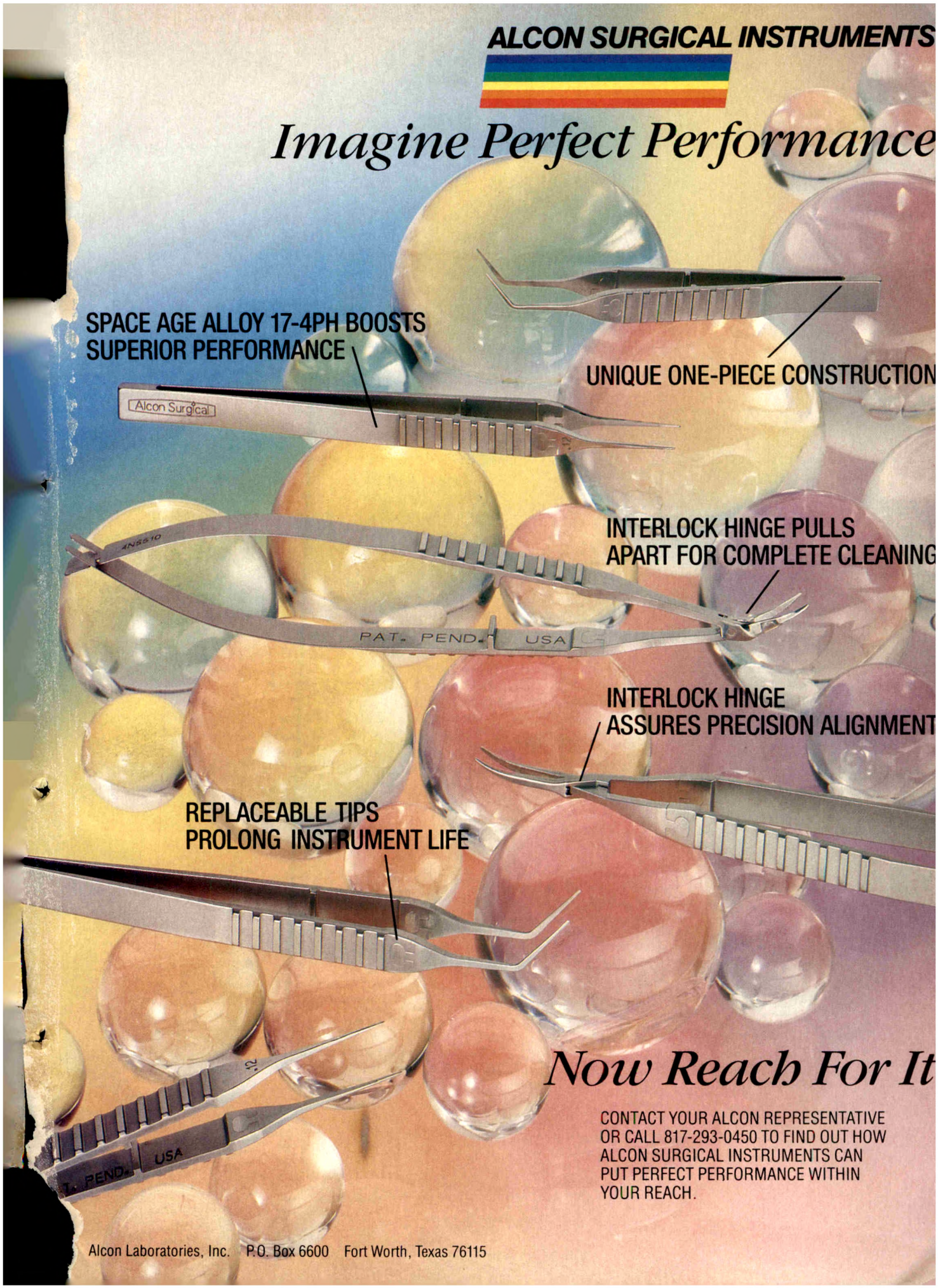
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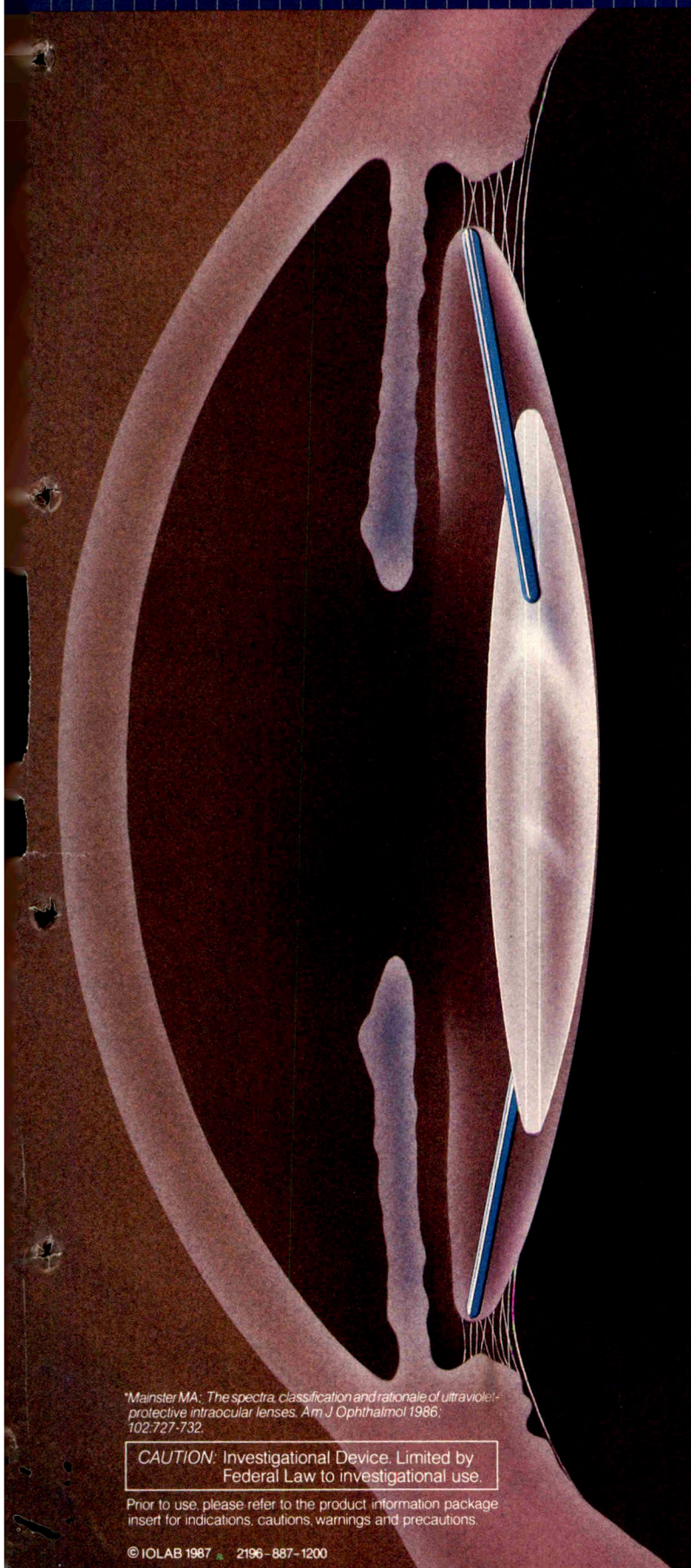
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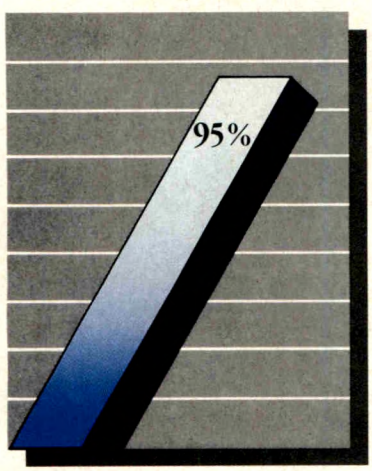
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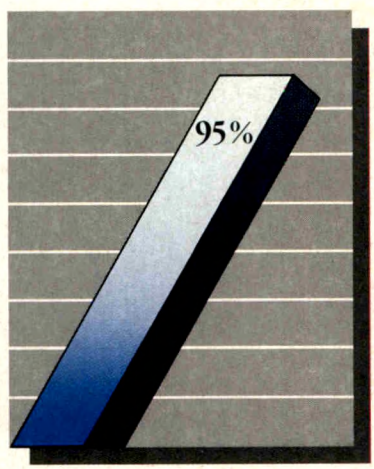
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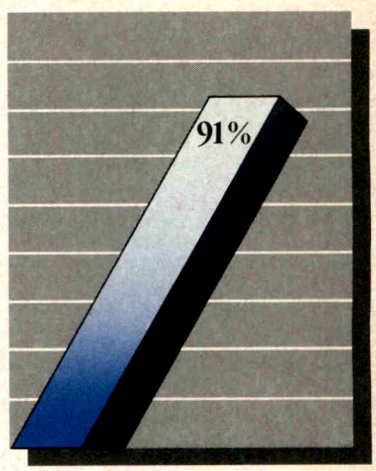
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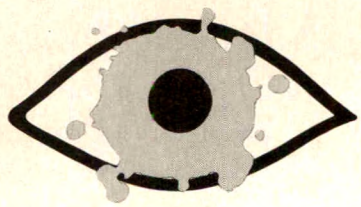


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- **Professor Alan Laties**, MD, Chairman, Scientific Advisory Board RP Foundation, USA and long-time leader of international and US RP research.
- **Professor John Marshall**, medical and research advisor to the British RP Society, leader of international and UK RP research.
- **Professor Robert Williamson**, one of the world's leading authorities on mapping human inherited diseases.
- Dr Shomi Bhattacharya, leading authority on human genetics. The first genetic researcher to locate a DNA marker linked to RP.
- Dr Eliot Berson, researcher in clinical and diagnostic studies on RP, and leading US RP clinician and researcher.
- Dr Mike Boulton, leading UK researcher on tissue culture and RP.
- Dr Gail Bruns, leading US genetic researcher.
- Professor Barry Cole, Australian and internationally-renowned vision research leader.
- Professor Ian Constable, leading Australian ophthalmic researcher.
- Dr Kay E Davies, leading UK human geneticist.
- Dr Michael Denton, leading Australian RP genetic researcher.
- Dr Frank Halliday, Retinal Dystrophy Service, Sydney.
- Dr Joe G Hollyfield, leading US ophthalmic RP researcher.
- Dr Marcelle Jay, world leader in RP Ophthalmic genetic registers.
- Professor M LaVail, leading US ophthalmic researcher.
- Professor Ray Over, La Trobe University, Melbourne, researcher on psychology of RP.
- Drs John & Shirley Sarks, Sydney, leading researchers on the pigment epitheleum, clinical and pathological RP studies.
- Dr Max Zrenner, leading European RP researcher.

INVITATION TO SUBMIT PAPERS/POSTERS

1. Submission of papers

(a) The RP Congress invites the submission of papers for consideration at its Melbourne Congress.
(b) Papers/posters should not exceed 2,000 words.
(c) A summary of papers should be forwarded by airmail to RP Congress not later than February 29, 1988.
Original manuscripts and three copies should be forwarded by airmail not later than August 30, 1988.

The Congress Committee reserves the right to allocate papers to the most appropriate part of the program and to determine whether presentation will be by paper or poster.

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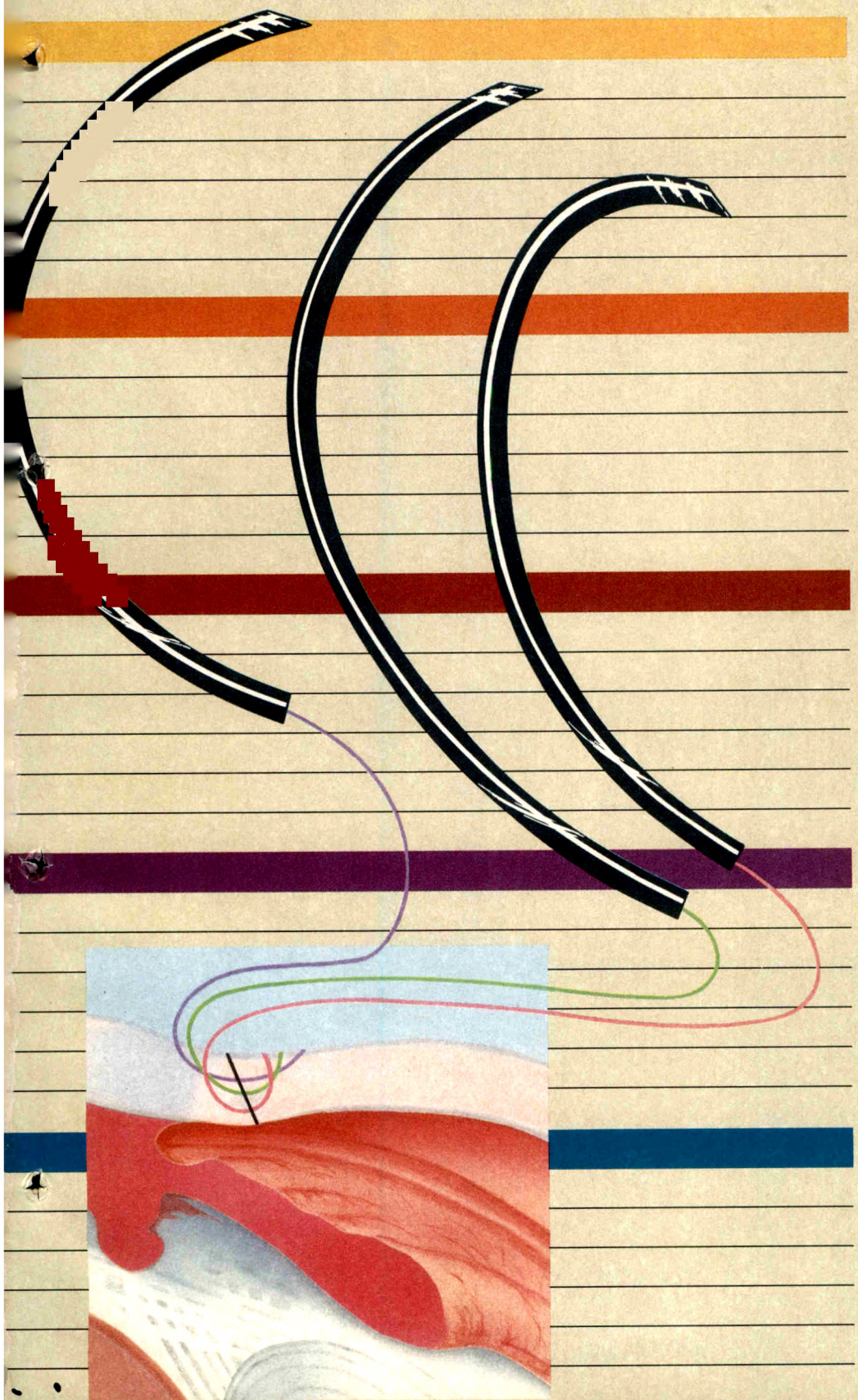
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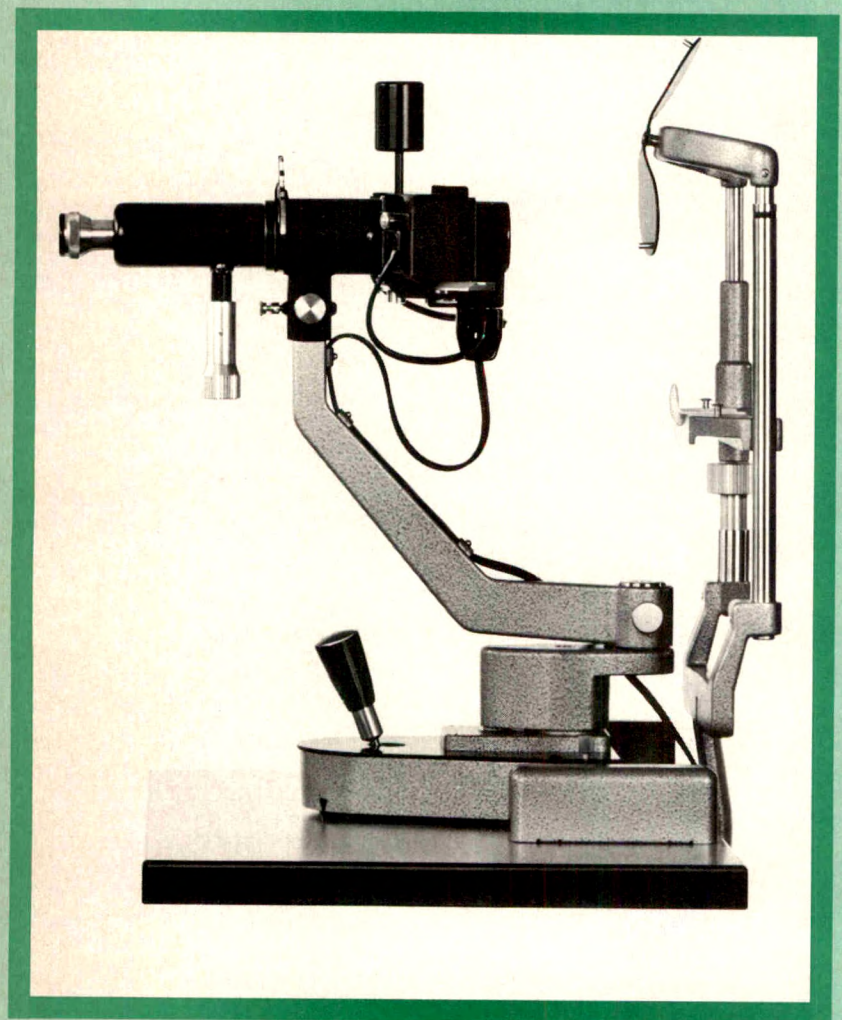
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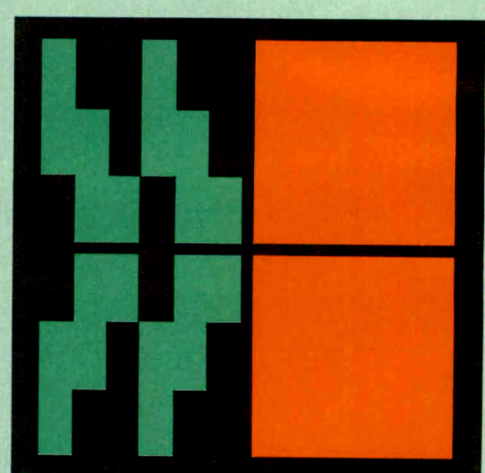
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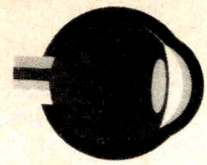
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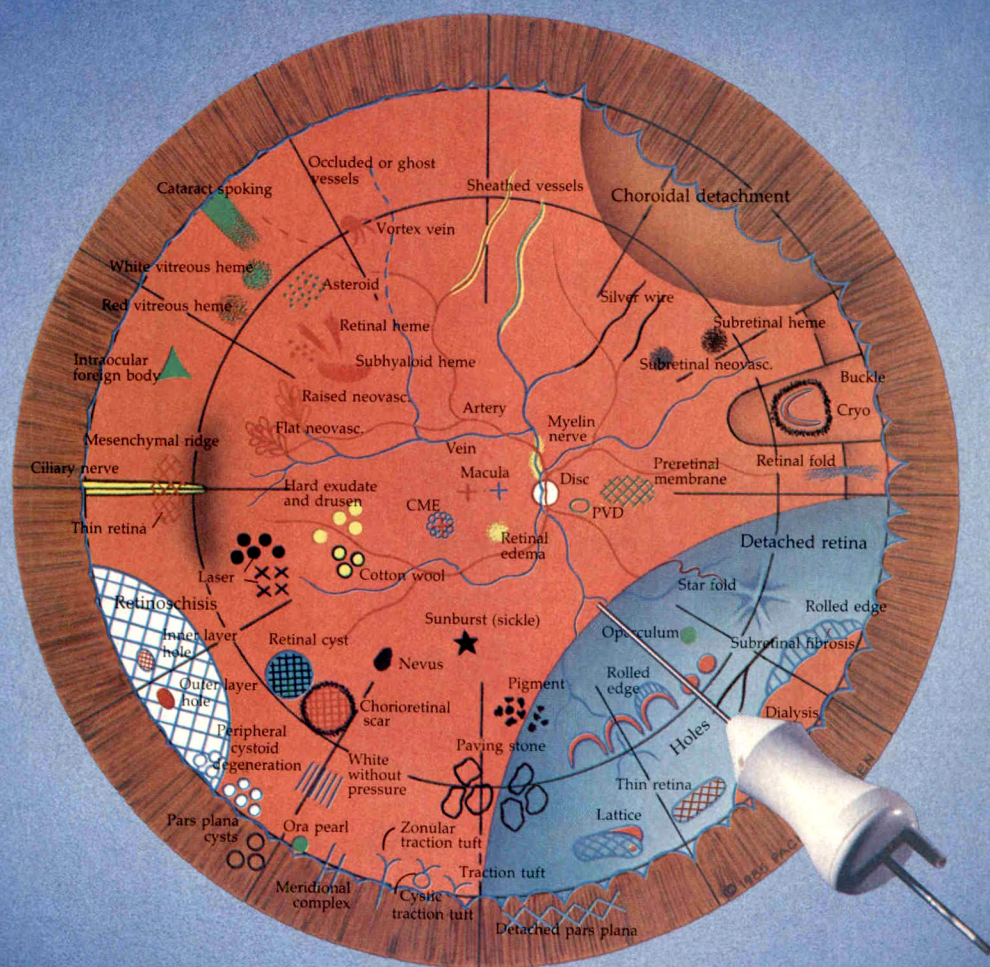
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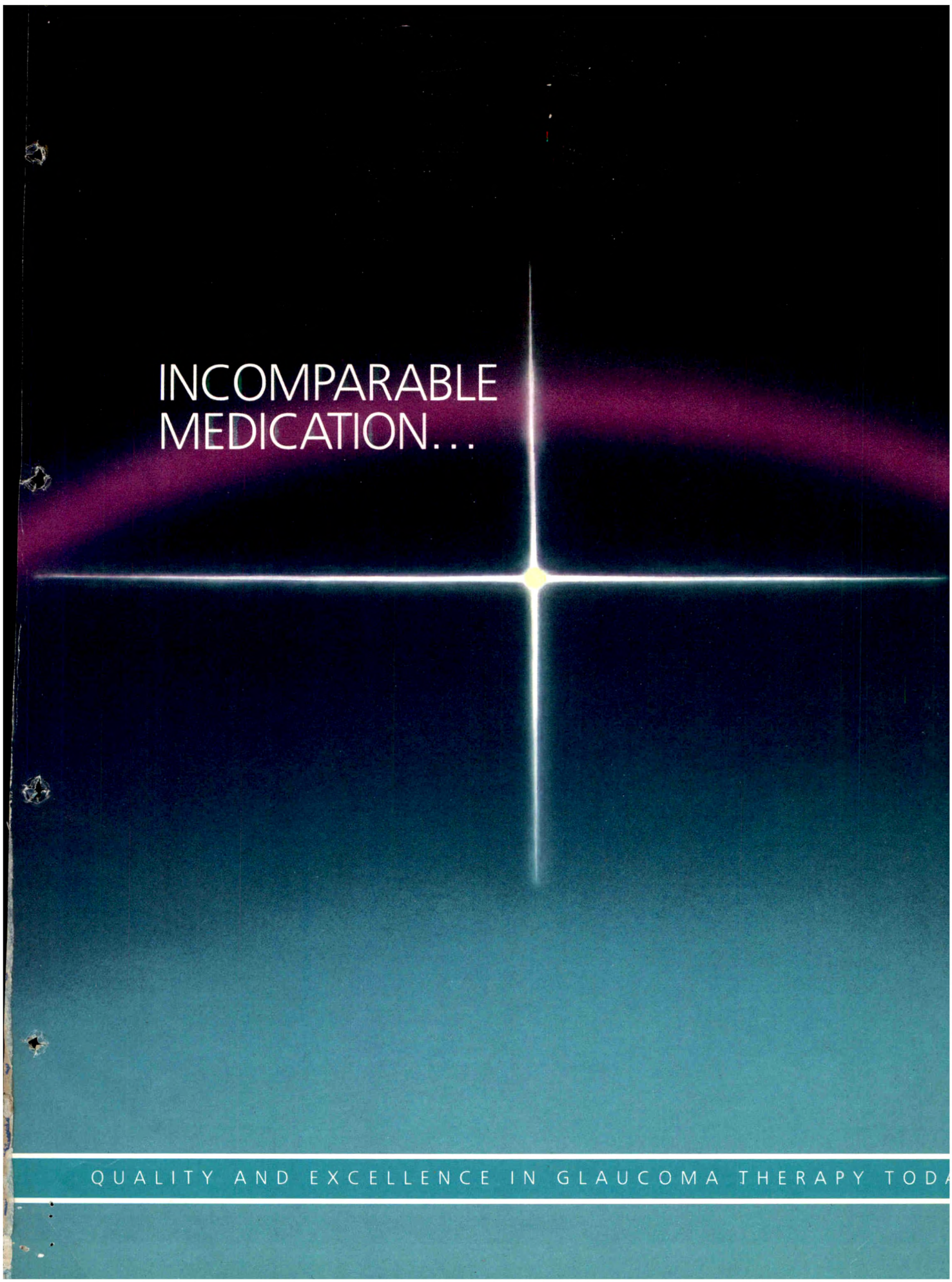
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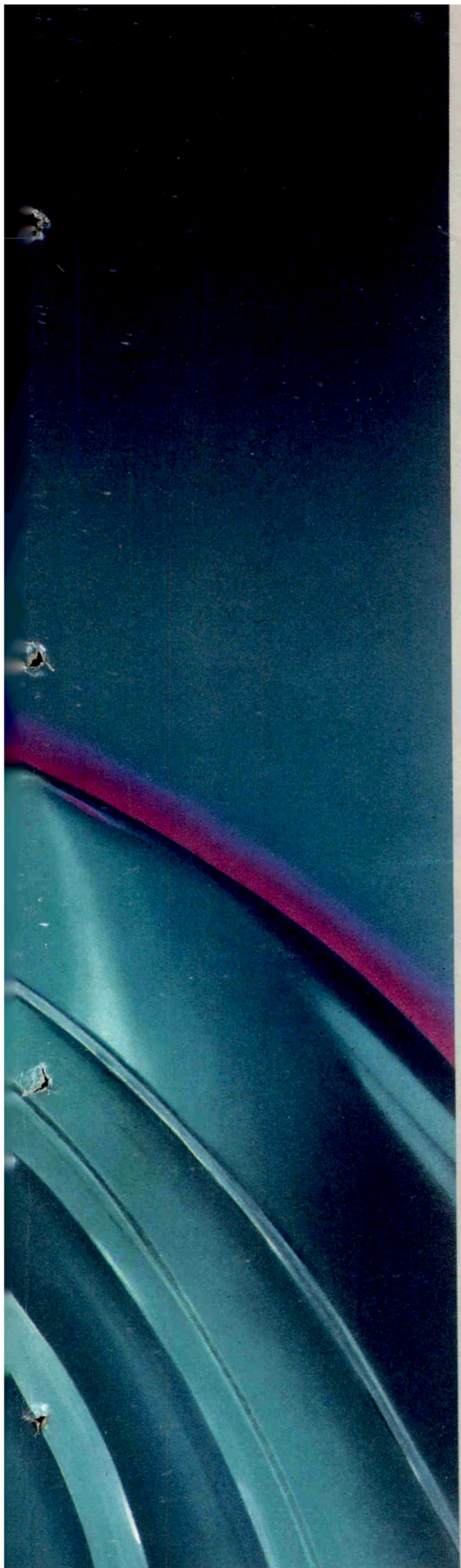
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Unsurpassed Ocular Tolerability

Of 110 subjects evaluated:

- nearly twice as many experienced burning or tearing with Betoptic** (betaxolol HCl)
- ocular symptoms overall were fewer and significantly less severe with TIMOPTIC

Preferred over Betoptic by More Than 6 to 1

Of 113 subjects evaluated:

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In clinical trials lasting from one month to over three years†...

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- 98% reported NO cardiovascular side effects
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Unsurpassed IOP Control Now... and for the Long Term

Efficacy findings revealed a significant reduction in IOP and no evidence of tachyphylaxis or tolerance.††

Consider the Outstanding Value of TIMOPTIC...

Efficacy, tolerability, ocular comfort, preference...plus the round OCUMETER® Sterile Ophthalmic Dispenser with the exclusive precision-designed tip that delivers a metered dose—dose after dose—to help make every drop of TIMOPTIC count for your patient.

*Data from a multiple-dose, double-masked, randomized, two-period crossover study of healthy volunteers comparing TIMOPTIC 0.5% b.i.d. to Betoptic 0.5% b.i.d. for ocular tolerability and subject preference.

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†Data from the original clinical trials for TIMOPTIC and from ongoing studies designed to assess the effects of TIMOPTIC, of pilocarpine, or of no treatment on long-term control of IOP and on change in visual fields. These studies are intended to have patients under observation for up to six years, with evaluations at three- to four-month intervals.

††All patients did not contribute data at all time points because the trials varied in length and not all patients were evaluated at each time period. The measurement at each time period represents the mean IOP of all patients available.

For the majority of patients with chronic open-angle glaucoma or elevated IOP who are at sufficient risk to require therapy

TIMOPTIC®

(TIMOLOL MALEATE) MSD

STERILE OPHTHALMIC SOLUTION

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How to start patients on TIMOPTIC:
Usual starting dosage: one drop 0.25% TIMOPTIC in the affected eye(s) twice a day.

How to transfer from another topical ophthalmic beta-adrenergic blocking agent to TIMOPTIC:
1. On the first day, after proper dosing, discontinue the topical agent being used.
2. On the second day, start treatment with one drop of 0.25% TIMOPTIC in the affected eye(s) b.i.d.

How to transfer from a single antiglaucoma agent (other than a topical ophthalmic beta-adrenergic blocking agent) to TIMOPTIC:
1. On the first day, continue with the agent already being used and add one drop 0.25% TIMOPTIC in the affected eye(s) b.i.d.
2. On the second day, discontinue the previously used agent and continue with TIMOPTIC in the affected eye(s) b.i.d.

How to transfer from several concomitantly administered antiglaucoma agents to TIMOPTIC:
1. If any agent is an ophthalmic beta-adrenergic blocker, discontinue before starting TIMOPTIC.
2. Continue the other agents being used, but add one drop of 0.25% TIMOPTIC to the affected eye(s) b.i.d.
3. On the following day, discontinue one of the other antiglaucoma agents.
4. The remaining antiglaucoma agents may be decreased or discontinued according to the patient's response to treatment.

If clinical response is not adequate:
Dosage may be increased (from the 0.25% solution) by changing to one drop 0.5% TIMOPTIC twice a day in the affected eye(s). Dosages above one drop of 0.5% TIMOPTIC twice a day generally have not been shown to produce further reduction of IOP. If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s).

In patients with a history of severe cardiac disease, signs of cardiac failure should be watched for and pulse rates should be checked.

CONTRAINDICATIONS: TIMOPTIC is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to any component of this product.

WARNINGS: As with other topically applied ophthalmic drugs, this drug may be absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death in association with cardiac failure, have been reported following administration of TIMOPTIC (see CONTRAINDICATIONS).

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, TIMOPTIC should be discontinued.

Obstructive Pulmonary Disease: PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (e.g., CHRONIC BRONCHITIS, EMPHYSEMA) OF MILD OR MODERATE SEVERITY, BRONCHOSPASTIC DISEASE OR HISTORY OF BRONCHOSPASTIC DISEASE (OTHER THAN BRONCHIAL ASTHMA OR HISTORY OF BRONCHIAL ASTHMA, IN WHICH 'TIMOPTIC' IS CONTRAINDICATED, see CONTRAINDICATIONS), SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS, INCLUDING 'TIMOPTIC'. However, if TIMOPTIC is necessary in such patients, then the drug should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of β_2 receptors.

Major Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution to patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

PRECAUTIONS: *General:* Patients who are receiving a beta-adrenergic blocking agent orally and TIMOPTIC should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Patients should not receive two topical ophthalmic beta-adrenergic blocking agents concurrently.

Because of potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with TIMOPTIC, alternative therapy should be considered.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. TIMOPTIC has little or no effect on the pupil. When TIMOPTIC is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone.

As with the use of other antiglaucoma drugs, diminished responsiveness to TIMOPTIC® (Timolol Maleate, MSD) after prolonged therapy has been reported in some patients. However, in one long-term study in which 96 patients have been followed for at least three years, no significant difference in mean intraocular pressure has been observed after initial stabilization.

Drug Interactions: Although TIMOPTIC used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with TIMOPTIC and epinephrine has been reported occasionally.

Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Caution should be used in the coadministration of beta-adrenergic blocking agents, such as TIMOPTIC, and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Animal Studies: No adverse ocular effects were observed in rabbits and dogs administered TIMOPTIC topically in studies lasting one and two years respectively.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year oral study of timolol maleate in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human oral dose* (1 mg/kg/day). Similar differences were not observed in rats administered oral doses equivalent to 25 or 100 times the maximum recommended human oral dose. In a lifetime oral study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages up to 60 mg timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/mL). In Ames tests, the highest concentrations of timolol employed, 5000 or 10,000 μg/plate, were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human oral dose.

Pregnancy: Pregnancy Category C: Teratogenicity studies with timolol in mice and rabbits at doses up to 50 mg/kg/day (50 times the maximum recommended human oral dose) showed no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (1,000 times the maximum recommended human oral dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 100 times the maximum recommended human oral dose, in this case without apparent maternotoxicity. There are no adequate and well-controlled studies in pregnant women. TIMOPTIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established by adequate and well-controlled studies.

ADVERSE REACTIONS: TIMOPTIC Ophthalmic Solution is usually well tolerated. The following adverse reactions have been reported either in clinical trials of up to three years' duration prior to release in 1978 or since the drug has been marketed.

BODY AS A WHOLE: Headache, asthenia, chest pain. CARDIOVASCULAR: Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, palpitation, cardiac arrest. DIGESTIVE: Nausea, diarrhea. NERVOUS SYSTEM/PSYCHIATRIC: Dizziness, depression, increase in signs and symptoms of myasthenia gravis, paresthesia. SKIN: Hypersensitivity, including localized and generalized rash, urticaria. RESPIRATORY: Bronchospasm (predominantly in patients with preexisting bronchospastic disease), respiratory failure, dyspnea, nasal congestion. ENDOCRINE: Masked symptoms of hypoglycemia in insulin-dependent diabetics (see WARNINGS). SPECIAL SENSES: Signs and symptoms of ocular irritation, including conjunctivitis, blepharitis, keratitis, blepharoptosis, decreased corneal sensitivity, visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis.

Causal Relationship Unknown: The following adverse effects have been reported, and a causal relationship to therapy with TIMOPTIC has not been established: *Body as a Whole:* Fatigue; *Cardiovascular:* Hypertension, pulmonary edema, worsening of angina pectoris; *Digestive:* Dyspepsia, anorexia, dry mouth; *Nervous System/Psychiatric:* Behavioral changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence, and other psychic disturbances; *Skin:* Alopecia; *Special Senses:* Aphakic cystoid macular edema; *Urogenital:* Retroperitoneal fibrosis, impotence.

The following additional adverse effects have been reported in clinical experience with oral timolol maleate and may be considered potential effects of ophthalmic timolol maleate: *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Edema, worsening of arterial insufficiency, Raynaud's phenomenon, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting; *Hematologic:* Nonthrombocytopenic purpura; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating, cold hands and feet; *Musculoskeletal:* Arthralgia, claudication; *Nervous System/Psychiatric:* Vertigo, local weakness, decreased libido, nightmares, insomnia, diminished concentration; *Respiratory:* Rales, cough, bronchial obstruction; *Special Senses:* Tinnitus, dry eyes; *Urogenital:* Urination difficulties.

Potential Adverse Effects: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents and may be considered potential effects of ophthalmic timolol maleate: *Digestive:* Mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Agranulocytosis, thrombocytopenic purpura; *Nervous System:* Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Urogenital:* Peyronie's disease.

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis sicca, otitis, and sclerosing serositis attributed to the beta-adrenergic receptor blocking agent practolol. This syndrome has not been reported with timolol maleate.

HOW SUPPLIED: TIMOPTIC Ophthalmic Solution, 0.25% and TIMOPTIC Ophthalmic Solution, 0.5%. Both are available in 2.5-mL, 5-mL, 10-mL, and 15-mL plastic OCUMETER® ophthalmic dispensers with a controlled drop tip. **Also Available:** Preservative-free TIMOPTIC in OCUDOSE® (Dispenser) Sterile Ophthalmic Unit-Dose Dispenser (see separate Prescribing Information).

Storage: Protect from light. Store at room temperature.

*The maximum recommended single oral dose is 30 mg of timolol. One drop of TIMOPTIC 0.5% contains about 1/150 of this dose, which is about 0.2 mg.

MSD
MERCK SHARP & DOHME

For more detailed information, consult your MSD Representative and the Prescribing Information.
Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

J6TM24(426/303)

QUALITY AND EXCELLENCE IN GLAUCOMA THERAPY TODAY

WILLS EYE HOSPITAL
40TH ANNUAL CONFERENCE

Sponsored by the Wills Eye Hospital Society of Ex-Residents

OWEN BELMONT, M.D.
Conference Chairman

MARCH 17-18-19, 1988
ADAM'S MARK HOTEL
PHILADELPHIA, PA

BEDELL MEMORIAL LECTURE
"Ophthalmic Laser Surgery:
Past, Present, Future"
Professor Franz Fankhauser
University of Bern, Switzerland

IRVING H. LEOPOLD LECTURE
"Refractive Corneal Surgery:
Promises and Pitfalls"
George O. Waring III, M.D.
Emory University, Georgia

SYMPOSIA

VIRAL DISEASE SYMPOSIUM
Peter R. Laibson, M.D., *Moderator*

Panel:
Juan J. Arentsen, M.D.
L. Michael Cobo, M.D.
Elisabeth J. Cohen, M.D.
Michael A. Naidoff, M.D.
R. Doyle Stulting, M.D.

LASER SYMPOSIUM
Louis W. Schwartz, M.D., *Moderator*

Panel:
Hugh Beckman, M.D.
Prof. Franz Fankhauser
Jay L. Federman, M.D.
Stephen L. Trokel, M.D.

CATARACT SYMPOSIUM
Stephen B. Lichtenstein, M.D., *Moderator*

Panel:
Raymond E. Adams, M.D.
Jack T. Holladay, M.D.
John D. Hunkeler, M.D.
Daniel M. Kane, M.D.

WORKSHOPS

Cataracts
Cornea
Glaucoma
Medical-Legal
Neuro-Ophthalmology
Oculoplastic Surgery
Oncology
Pediatrics
Political Developments
Retina

Allied Assistants' Meeting	Thursday, 3/17/88
Ophthalmic Nurses' Meeting	Friday, 3/18/88
Basic Surgical Assisting	Saturday, 3/19/88

Over ninety (90) original papers will be presented by individual authors covering all aspects of the field of Ophthalmology. Spouse Program, including tour of the Pearl S. Buck House and Luncheon is scheduled for Thursday, March 17, 1988. Brun and meeting with jewelry artist, Agnes Wajdyk, is scheduled for Friday, March 19, 1988 at the Adam's Mark Hotel.

REGISTRATION INFORMATION

Practicing Physicians	$300.00	Allied Assistants' Meeting	$65.00
WEH Staff & Alumni	$250.00	Nurses' Meeting	$65.00
Retired Physicians	$100.00	Basic Surgical Assisting	$40.00
Residents & Fellows	$ 75.00	Spouse Program	$35.00

This Continuing Medical Education activity is accredited for 16 Credit Hours in Category I of the AMA. Credits will be granted for the Allied Assistants' Meeting and the Ophthalmic Nurses' Meeting.

For additional information please contact Jeanne L. Kiska, Meeting Manager, 1621 Norristown Road, Maple Glen, PA 19002 (215) 322-8950.

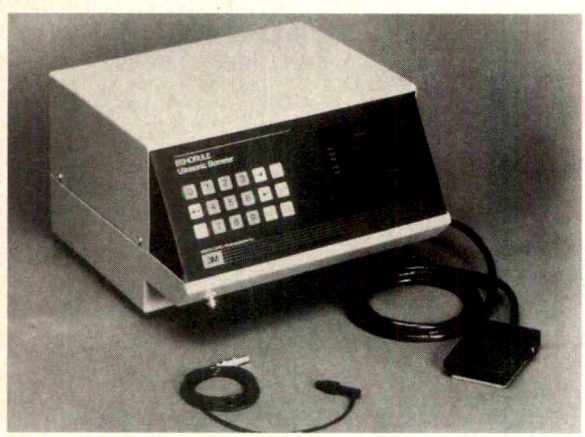
P 24 318

NEW PRODUCTS AND SERVICES

New products and services considered by the editors to be of interest to our readers are described on the basis of information supplied by the companies cited. Publication of these notices does not imply endorsement or warranty by The Ophthalmic Publishing Company, publishers of The American Journal of Ophthalmology, for these products and services.

Diagnostic Instruments

Phakosystems, Inc./3M
225-5N-03
3M Center
St. Paul, MN 55144-1000
Tel: (612) 736-0876

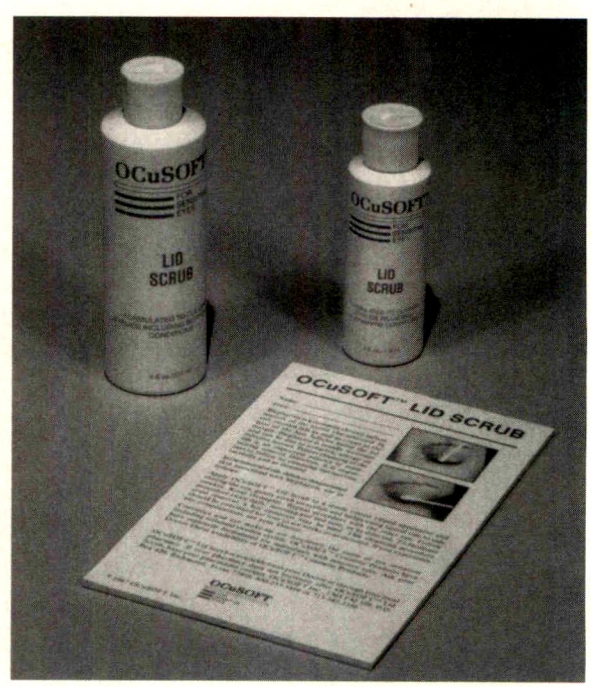


An ultrasound diagnostic instrument that provides precise measurements for use in planning surgical procedures has been introduced by Phakosystems, Inc., a subsidiary of 3M Vision Care. The Echorule brand Ultrasonic Biometer measures anterior eye chamber depth, lens thickness, and axial length in millimeters. Supplied with the patient's keratometry reading and intraocular lens "A constant," the instrument also will calculate the exact dioptric power of the IOL required with SRK II and Binkhorst formulas to obtain the desired postoperative refraction.

Designed for use in the surgeon's office, the Echorule instrument is equipped with a printer that produces a hard-copy record of data for the patient file.

Patient Care Products

OCuSOFT, Inc.
1305 FM359
P.O. Box 429
Richmond, TX 77469
Tel: (800) 233-5469 (National)
(713) 342-3350 (Texas)



OCuSOFT, Inc., manufacturer of OCuSOFT Lid Scrub, an eyelid cleanser formulated to assist in the treatment of blepharitis, announces the availability of Patient Instruction Pads. These instruction pads, written in English and Spanish, contain tear-away information sheets on blepharitis as well as instruction in the use of OCuSOFT Lid Scrub. They are provided free of charge to physicians as a patient education service.

OCuSOFT Lid Scrub removes oils, debris, and desquamated skin associated with blepharitis. OCuSOFT Lid Scrub does not require shaking. OCuSOFT Lid Scrub is available in both a 4-oz and 8-oz size. The 4-oz bottle is priced at $2.95.

We've put taste more accurate acuity testing...



right at your fingertips!

The Mentor B-VAT™ II Video Acuity Tester – fast, accurate, with instantaneous displays of 9 different optotypes at the touch of your finger. The system also provides the option to display the optotypes in random sequences, eliminating memorization and speeding up patient acuity testing, even illiterates and children. Levels of contrast can be varied on all optotypes.

Hand held controller displays what patient sees – B-VAT II includes a high contrast video monitor plus a control module with an LCD readout of the monitor display, allowing the examiner to observe the patient throughout the examination.

U.S. Patent No. 4239351



There are over 50 functions including red-green. The control unit also includes provisions for prescription adding using B-VAT II's built-in computer. The system can be adjusted down to 10 ft. lanes.

B-VAT II is priced at under $4,000.

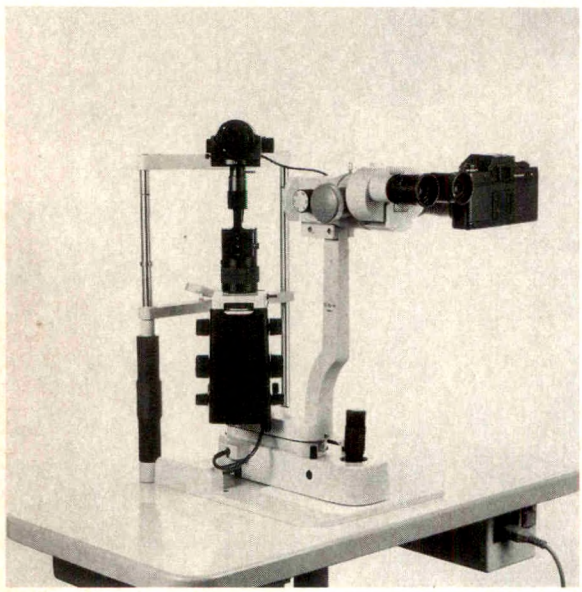
For more information, please write or call toll free:

(National) **1-800-992-7557**
(Collect in Mass.) **1-617-871-6950**

MENTOR
O&O, INC.
3000 Longwater Drive, Norwell, MA 02061

Cameras

Carl Zeiss, Inc.
One Zeiss Dr.
Thornwood, NY 10594
Tel: (800) 522-5204 (National)
(914) 681-7768 (New York)



A new SP 30 camera attachment is now available for the Zeiss 30 SL/M slit lamp. The camera attachment is ideal for brilliant slit image, survey and fluorescence photography, and can be retrofitted to any 30 SL/M slit lamp. The camera attachment accepts daylight films such as Ektachrome (400 ASA). Commercial flash lamps may be used; no separate fill-in flash is required. The device features continuous slit length from 2 to 8 mm, and slit width in steps from 0.2 to 8 mm.

Using the compact Zeiss Slit Lamp 30 SL/M, the operator can perform slit-lamp examinations, tonometry, and ophthalmoscopy with a single instrument. It features a rapid, five-step magnification changer (×5 to ×30), a large field of view of the cornea, and a continuous, progressive slit width from 0 to 9 mm. Prism head 0 to 20 degrees for continuous setting of the axis of illumination from the horizontal permits all types of examinations.

Surgical Devices

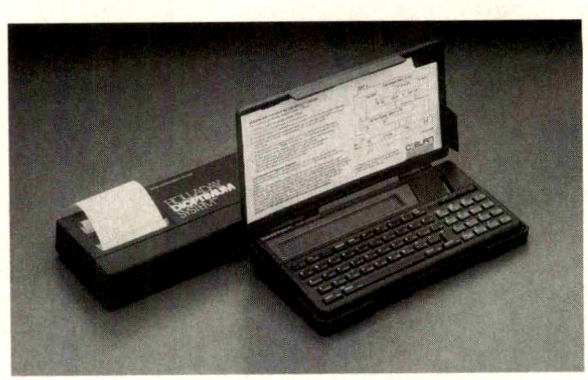
Keeler Instruments, Inc.
456 Parkway
Broomall, PA 19008
Tel: (800) 523-5620 (National)
(215) 353-4350 (Pennsylvania)



Keeler Instruments has introduced the ACU 22XT, a nonelectric cryo system, which features rapid freeze/defrost with cataract and vitreous probes that operate with end of tip freeze only. The console displays tip temperature for retinal and glaucoma procedures. Purging is automatic.

Intraocular Lenses

Coburn Intraocular Lenses
1375 S. Fort Harrison
Clearwater, FL 33517
Tel: (800) 237-5906 (National)
(800) 282-1208 (Florida)



Coburn Intraocular Lenses has announced the availability of the Dioptimum System, developed in association with Dr. Holladay. This system delivers

VISITEC

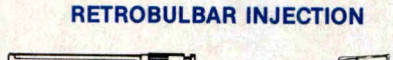
for all the right reasons

VISITEC® OFFERS THE FIRST COMPLETE LINE OF OPHTHALMIC DISPOSABLE PRODUCTS DESIGNED FOR ECCE SURGICAL PROCEDURES AND PATIENT CARE

- Sterile - ready for use - minimizes set up time - open when needed
- Single use - assures optimum product performance during delicate microsurgical procedures and patient care
- Individually blister packed - products double sterile packed with easy open lid for sterile transfer
- Product identification - color coding and label assures the correct product and size
  Avoids errors and delays during valuable surgery time
- Compact dispenser packaging - easily stored and stocked

PRE-OP

RETROBULBAR INJECTION



1637 Retrobulbar Needle *(Atkinson)* (25g x 1½")

1638 Retrobulbar Needle *(Atkinson)* (23g x 1½")

IOP REDUCTION

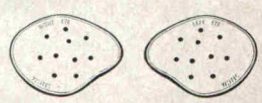


1025 Ocular Pressure Reducer Kit *(McCannel)*

1046 Ocular Pressure Reducer Kit with Pressure Gauge *(McCannel)*

POST-OP

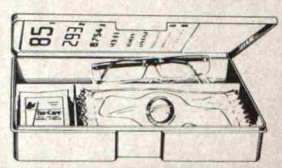
EYE PROTECTION



1019 VISITEC® Eye Shield

FOLLOW YOUR PATIENT HOME WITH POST-OP KITS

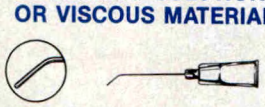
1050 Patient Post-Op Eye Care Kit



CUSTOM AND PERSONALIZED KITS AVAILABLE

ECCE PROCEDURES

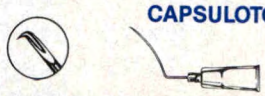
INJECTING AIR BUBBLE, IRRIGATING SOLUTION OR VISCOUS MATERIAL



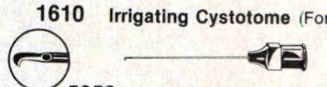
1273 Anterior Chamber *(Rycroft)* 30g

1273A Anterior Chamber *(Rycroft)* 27g

CAPSULOTOMY

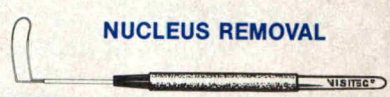


1610 Irrigating Cystotome (Formed) 25g



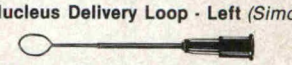
5053 Irrigating Sharp Cystotome 24g

NUCLEUS REMOVAL



5076R Nucleus Delivery Loop - Right *(Simcoe)*

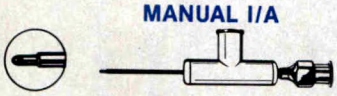
5076L Nucleus Delivery Loop - Left *(Simcoe)*



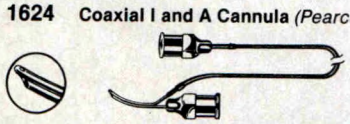
1619 Irrigating Vectis *(Pearce)* (25g)

CORTEX REMOVAL

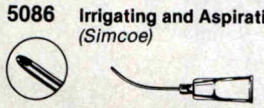
MANUAL I/A



1624 Coaxial I and A Cannula *(Pearce)*

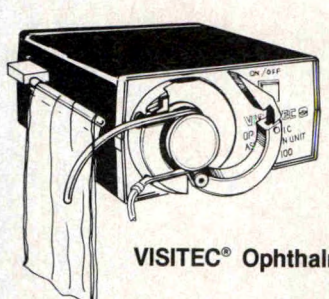


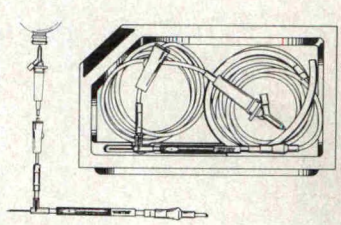
5086 Irrigating and Aspirating Cannula *(Simcoe)*



5075 VISITEC® Cortex Extractor 23g

AUTOMATED I/A



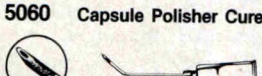


VISITEC® Ophthalmic Aspiration Unit Model 100
With
1035 VISIKIT® I/A Pack

CAPSULE POLISHING



5060 Capsule Polisher Curette *(Kraff)*



5071 VISITEC® Capsule Polisher 23g

IOL INSERTION



5063 Angled Lens Manipulating Hook *(Sinskey)*



5078 Lens Pusher *(Aker)*



5084 Angled Manipulating Hook *(Fenzl)*

ACCESSORY PRODUCTS



1037 VISITEC® Corneal Shield *(Hessburg)*



1033 VISITEC® IOL Glide *(Sheets)*



1034 VISITEC® IOL Glide *(Hessburg)*



1030 VISITEC® Fluid Filter 0.2 Micron



16516 Pro-Ophta Absorbent Sticks

CHOOSE VISITEC® FOR ALL YOUR SURGICAL NEEDS FOR PLANNED ECCE — FROM PRE-OP TO POST-OP

FOR COMPLETE CATALOG AND PRICES CONTACT:

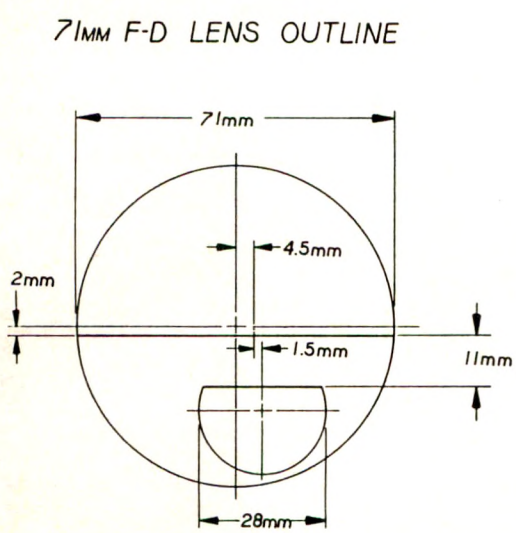
VISITEC COMPANY • 2043 WHITFIELD PARK DRIVE • SARASOTA, FLORIDA 34243 • 813-758-1428
800-237-2174 (OUTSIDE FLORIDA) • TELEX 5106000179

accurate intraocular lens power calculation. In addition to its data screening capabilities, the Dioptimum System allows each surgeon to develop a personalized surgeon factor to compensate automatically for built-in systematic errors in ultrasound and keratometric instrumentation or differences in their use; provide for differences in IOL optic and haptic designs; and adjust for individual differences in surgical technique.

The Dioptimum System comes with a portable computer, a printer for hard-copy results, software package, instruction manual, and leather carrying case.

Lenses

Optical Radiation Corp.
1300 Optical Dr.
Azusa, CA 91702
Tel: (800) 423-8561 (National)
(818) 969-1744 (California)



Orcolite, a division of Optical Radiation Corporation, has announced the release of the new FD Trifocal. The new lens, made of CR39, is designed for the patient who uses intermediate focal distances. The expanded intermediate segment provides easy viewing transition and is comfortable for everything from watching television, to viewing objects across the room, to reading fine print. The lightweight FD Trifocal is available in a 28-mm segment, with ultraviolet inhibitors, for a wide range of prescriptions.

Contact Lenses

Paragon Optical, Inc.
947 E. Impala Ave.
Mesa, AZ 85204
Tel: (800) 528-8279

A new, rigid gas permeable lens that offers higher oxygen transmissibility and resistance to protein deposits received recommendation from the Ophthalmic Panel of the Food and Drug Administration for premarket clearance for daily wear. The new lens, called FluoroPerm, is manufactured by Paragon Optical, Inc., and has a Dk of $92 \times 10 - 11$. The lens has high oxygen transmissibility and the fluorine content enhances the lens' ability to resist protein deposits. The lens is ideal for patients who have significantly high mucoid and lipid content in their tear chemistry or those who need a higher Dk.

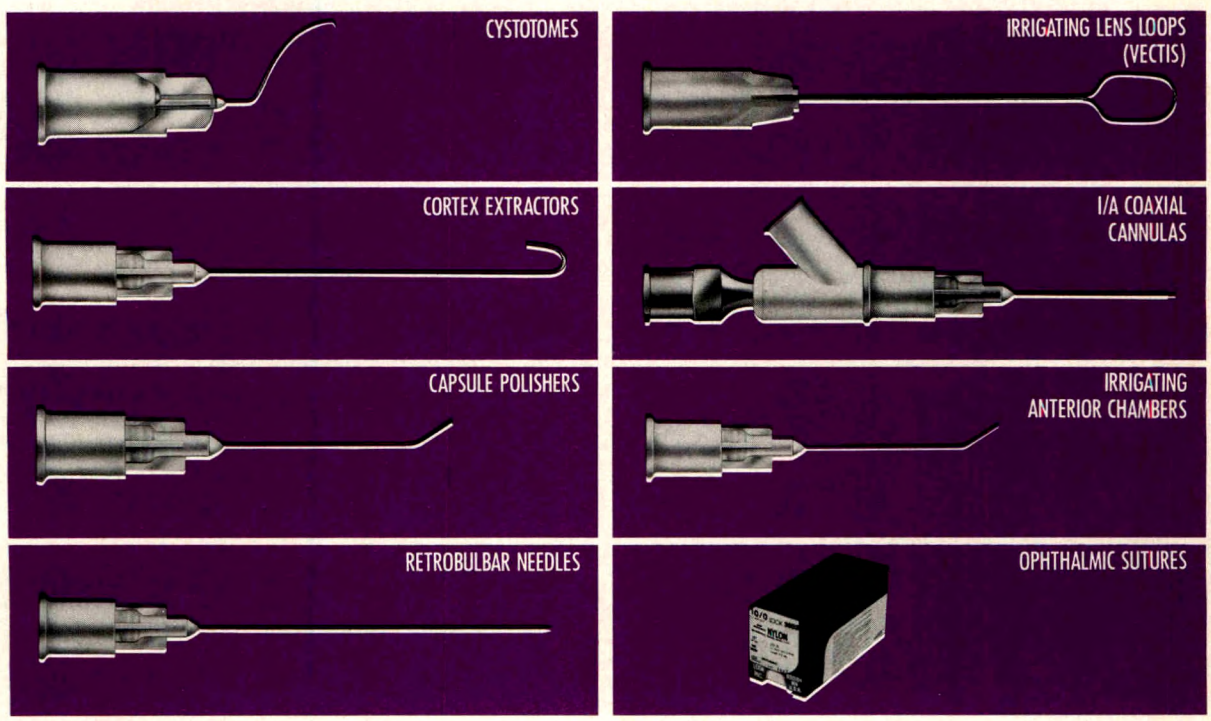
Low Vision Aids

Eschenbach Optik of America
25 November Trail
Weston, CT 06883
Tel: (203) 227-9409



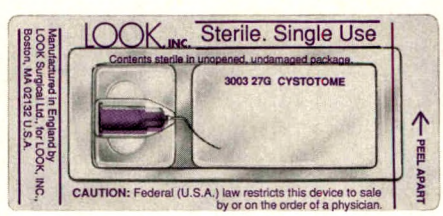
Eschenbach Optik of America has introduced Hi-Lites, an illuminated display designed for the offices of eyecare professionals and organized to showcase ten special vision aids and magnifiers. The illumination and styling of Hi-Lites are designed to attract the eye and stimulate the interest of the elderly and those who know people with low-vision problems

THE NEW LOOK OF DISPOSABLE OPHTHALMICS



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LOOK, INC.

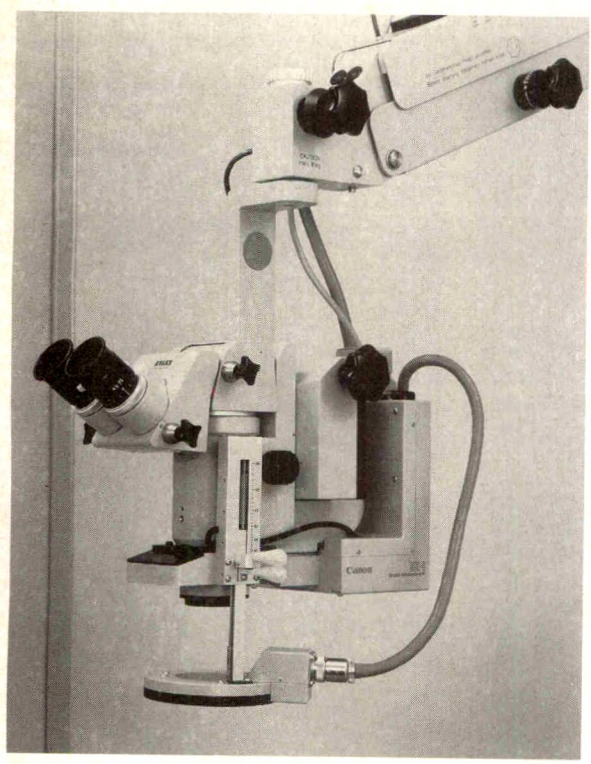
45 Charles Park Road • Boston MA 02132, U.S.A. • (617) 325-2112 • (800) 821-8349 • TELEX 940426

associated with age. The display includes three illuminated stand magnifiers; three stand magnifiers; three aspheric hand-held magnifiers; and a sight-enhancing bright field magnifier.

The ten vision aids plus the illuminated display are priced at $486.60 (order No. 2812-04).

Keratometers

Canon U.S.A., Inc.
One Jericho Plaza
Jericho, NY 11753-1679
Tel: (516) 933-6300

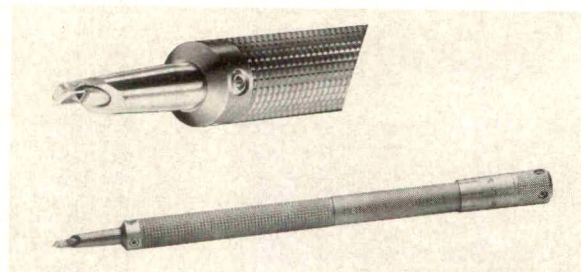


The new Canon SK-1 Surgical Auto Keratometer provides quick and accurate keratometry readings automatically during surgery. The SK-1 measures the radius of curvature, corneal refractive power, axis of the cornea, and corneal astigmatism in thousandths of a second during suturing. Results of measurements, which are displayed by LED and can be printed out, are taken by using a foot switch. A built-in memory allows instantaneous recall of the patient's preoperative readings. Measurements can also be made of the peripheral area and the center of the cornea.

The SK-1 attaches easily and quickly to several Zeiss surgical microscopes. No modifications to the microscope are necessary and the SK-1 does not interfere with microscope functions.

Surgical Instruments

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A Reassessment of Infantile Esotropia
XLIV Edward Jackson Memorial Lecture

Gunter K. von Noorden, M.D.

Essential infantile esotropia is an early acquired, not a congenital, condition, although congenital factors may favor its development between the ages of 3 and 6 months. It must be distinguished from other forms of esotropia with an onset between birth and the first six months of life. The cause of essential infantile esotropia remains unknown, but advances in our knowledge can be expected from the rapidly emerging discipline of infant psychophysics. In analyzing treatment results, a clear distinction must be made between normal, subnormal, and anomalous forms of binocular cooperation. While complete restoration of normal binocular function is rarely, if ever, achieved, anomalous binocular cooperation has many functional advantages over suppression or diplopia and should not be disturbed by overzealous treatment. Subnormal binocular vision is considered to be an optimal, microtropia a desirable, and a residual small angle heterotropia an acceptable end stage of surgical therapy.

In a study of 358 surgically treated patients with a documented onset of essential infantile esotropia before age 6 months, subnormal binocular vision was present in 71 (20%), a microtropia in 25 (7%), and a small angle esotropia or exotropia in 140 (39%) of the patients. Surgical alignment before completion of the second year of life improved the chances for an optimal treatment result. However, conclusion of surgical treatment after the age of 2 or even 4 years did not preclude the development of binocularity on a subnormal or anomalous basis in many patients.

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Juxtapapillary Choroidal Neovascularization in Older Patients

Jane C. Kies, M.D., and Alan C. Bird, M.D.

We studied retrospectively 55 eyes with juxtapapillary choroidal neovascularization in 42 patients over the age of 50 years. In all but four lesions, the choroidal neovascularization was undetected, causing the choroidal new vessel complexes to be ill defined, discontinuous, and show irregular dye leakage on fluorescein angiography. Growth of the lesion was unpredictable. Visual loss occurred in eight of 16 eyes during the first six months of follow-up. Recurrent neovascularization after photocoagulation originated in some patients from outside the pretreatment subretinal complex. Of the 15 patients with bilateral involvement, 13 had juxtapapillary lesions. Fellow eyes in patients with unilateral juxtapapillary lesions showed no predisposing abnormality at or near the nerve head. The prevalence, density, and fluorescein angiographic characteristics of drusen were different from those in age- and sex-matched patients with macular neovascularization.

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Role of the Vitreous in Branch Retinal Vein Occlusion

Masanori Kado, M.D., and Clement L. Trempe, M.D.

We analyzed the vitreous findings in 62 patients (62 eyes) with major branch retinal vein occlusion to determine whether vitreous examination was useful in predicting the development of retinal or disk neovascularization, or both. In 18 eyes with no or partial posterior vitreous detachment and large areas of capillary nonperfusion (5 disk diameters or more), ten eyes (55.6%) eventually developed neovascularization. Only three of the remaining 44 eyes (6.8%) developed neovascularization. The probability of this development was greater in eyes with no or partial posterior vitreous detachment at the initial vitreous examination ($P = .0177$, Cox's regression analysis), and in those with large areas of nonperfusion ($P = .0097$, Cox's regression analysis).

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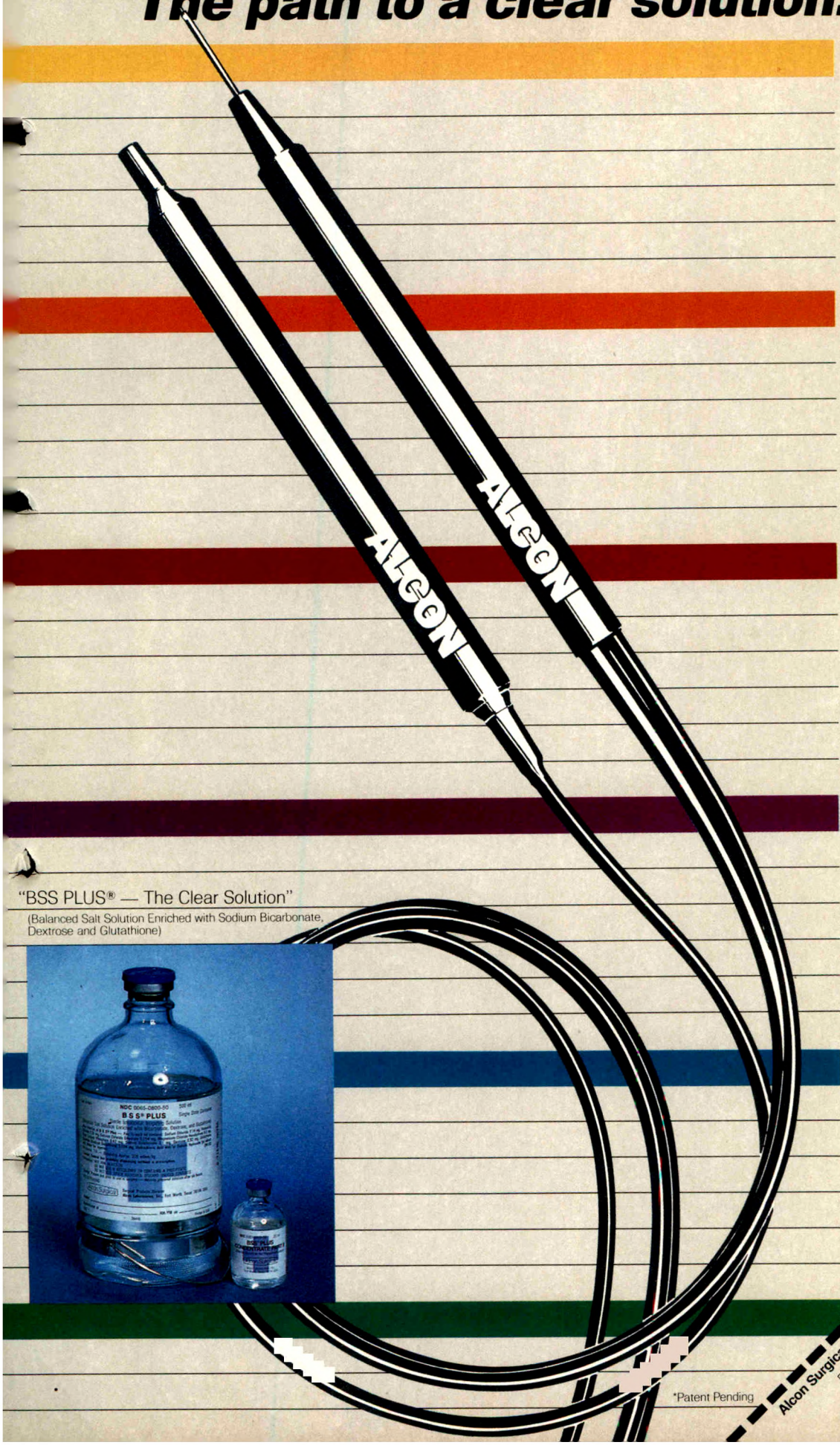
Vitreous Surgery for Hemorrhagic and Fibrous Complications of Age-Related Macular Degeneration

Eugene de Juan, Jr., M.D., and Robert Machemer, M.D.

We applied vitreous surgical techniques in the treatment of hemorrhagic and fibrous complications of choroidal neovascular membranes by removing subretinal scars or hemorrhage, or both, in four patients. The surgical goals were achieved in all patients. Visual acuity improved in three patients. The major complication was recurrent detachment associated with large retinotomies.

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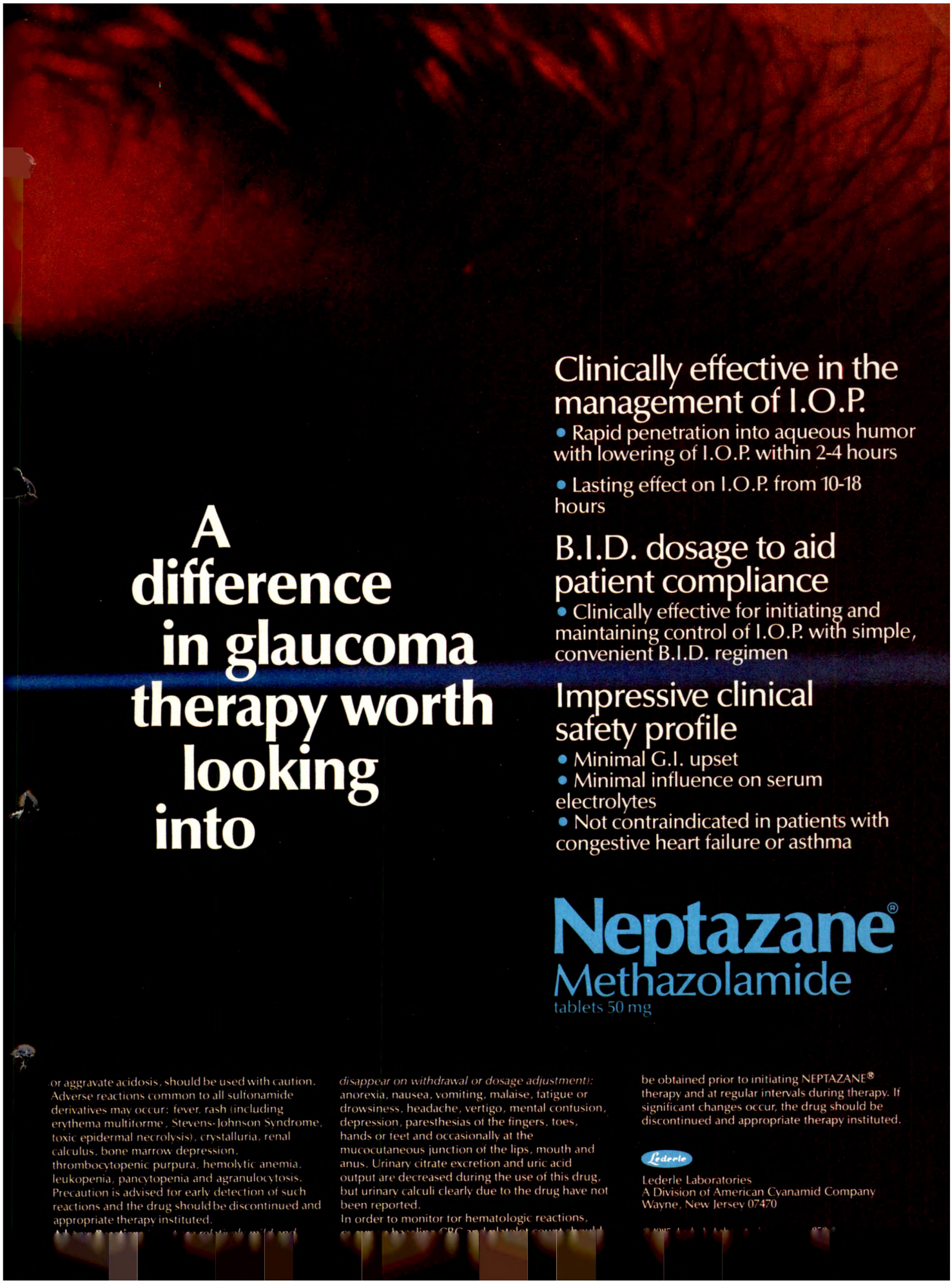
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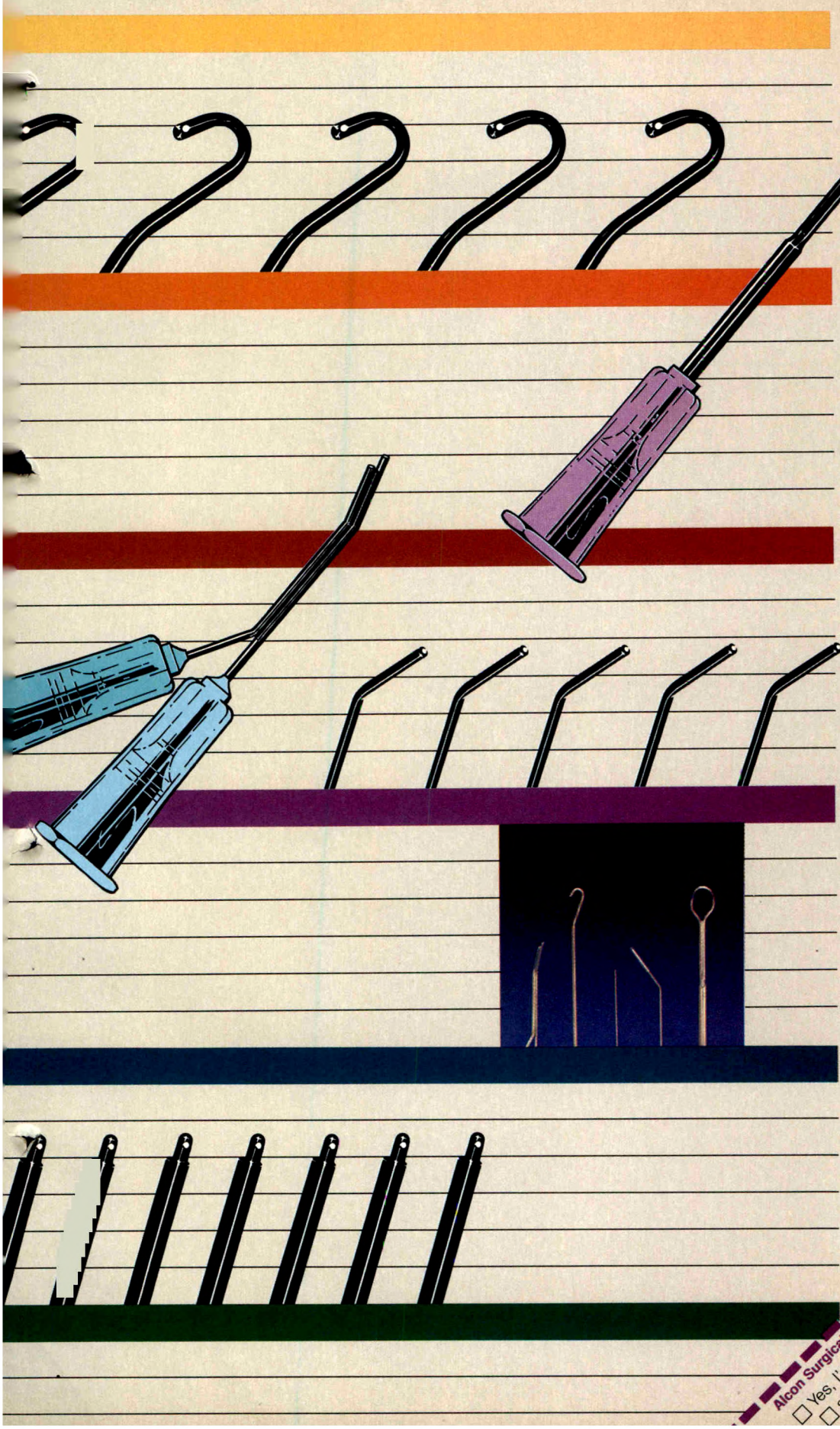
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A Reassessment of Infantile Esotropia
XLIV Edward Jackson Memorial Lecture

Gunter K. von Noorden, M.D.

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From the Cullen Eye Institute, Baylor College of Medicine and the Ophthalmology Service, Texas Children's Hospital, Houston, Texas. This study was supported in part by grants EY01120, EY07001, and EY02520 from the National Institutes of Health, and the Houston Delta Gamma Foundation, Houston, Texas. Presented at the 92nd American Academy of Ophthalmology Meeting, Dallas, Texas, Nov. 9, 1987.

Reprint requests to G. K. von Noorden, M.D., Ophthalmology Service, Texas Children's Hospital, Box 20269, Houston, TX 77225.

EDWARD JACKSON, M.D., was born in 1856 and received his medical degree from the University of Pennsylvania. His rapid emergence as a teacher, scientist, and clinician was soon recognized and he became Professor of Ophthalmology at the Philadelphia Polyclinic and surgeon at Wills Eye Hospital. He continued his brilliant career as professor and chairman at the University of Colorado Department of Ophthalmology in Denver, a position he held until his retirement in 1921. His broad interests encompassed the entire field of ophthalmology. To the ever-increasing chain of medical literature, Dr. Jackson has, to use his own happy phrase, added many shiny links. He wrote nearly 600 papers and four books and made many original contributions to the fields of strabismus and physiological optics. Jackson was one of the most prominent figures in American Ophthalmology of his time. He was president of the Academy of Ophthalmology, cofounder of the American Board of Ophthalmology and its first chairman, founder of the Ophthalmic Publishing Company, and editor of THE AMERICAN JOURNAL OF OPHTHALMOLOGY from 1918 to 1927.

Only one previous Jackson Lecture was concerned with strabismus and was presented 40 years ago by the late Francis Heed Adler.[1] Progress in the treatment of strabismus has been slow as compared to the development of

new techniques and instrumentation that have revolutionized surgery of the anterior and posterior segments in recent years. Advancements in strabismus have been less spectacular than they have been profound, not so much linked to advances in technology than to a better understanding of the pathophysiology. Through clinical research and introduction of new diagnostic methods and through collaboration with basic scientists, the pathophysiology of many forms of strabismus is better understood now and treatment is more effective than in the past. Among the ocular motility disorders in which our thinking has undergone substantial changes is infantile esotropia, formerly called congenital esotropia.

Terminology and Prevalence

Until Costenbader[2] introduced the term infantile esotropia to describe esotropia with an onset during the first year of life, the designation "congenital" was widely used and is still being used by many investigators today. Is this condition truly congenital, that is, existing at or dating from birth? If so, an infant would have no chance of experiencing a normal visual environment until the eyes are aligned. In view of the ever increasing body of knowledge from animal experiments and human research about the extraordinary sensitivity of the immature visual system to abnormal visual input, a congenital onset would have far-reaching implications regarding the chances for functional restoration of binocular vision. Conversely, if this type of esotropia has an onset between the age of 3 and 6 months, the abnormal condition would have been preceded by a period of normalcy during which the binocular visual connections would have had an opportunity to become, however loosely, established.

To answer the question of whether the onset of this strabismus is truly congenital, Nixon and coworkers[3] examined 1,219 normal alert infants in a newborn nursery. Exotropia and, less frequently, intermittent esotropia were present in one third of these babies shortly after birth. However, these conditions were no longer evident upon reexamination at the age of 6 months. No infant displayed the typical signs of congenital esotropia at birth. Only three patients in this group, who were orthotropic or exotropic at birth, had developed a constant esotropia when reexamined by the age of six months (E. M. Helveston, M.D., oral communication, Aug. 22, 1987). Similar results were independently obtained by Friedrich and de Decker.[4]

We have learned from these studies that infantile esotropia occurs less frequently than previously assumed and that its prevalence is probably closer to 0.1% than the estimated 1% of the population.[5,6] Moreover, this type of strabismus is an early acquired rather than an innate condition. Other authors had mentioned this possibility.[7,8] This does not exclude that a genuine congenital esotropia may occasionally occur, nor that a congenital defect contributes to the development of infantile esotropia. In view of these findings, I prefer the term "infantile" esotropia to describe a constant esotropia with a documented onset during the first six months of life and add the prefix "essential" to emphasize the unknown origin and to distinguish it from other forms of esotropia that occur at birth or during infancy.

Clinical Characteristics and Differential Diagnosis

Although Costenbader[2] listed the clinical findings in 500 patients with infantile esotropia, some confusion has persisted as to the characteristics and associated anomalies one may consider typical for this entity. I have accepted the classification (Table 1) arrived at during an informal gathering of North American and European strabismologists in Modena, Italy, May 24, 1984. To study the prevalence of associated clinical findings in essential infantile esotropia in our patient population, we reviewed the records of 408 patients treated on the Pediatric Ophthalmology Service of the Cullen Eye Institute, Baylor College of Medi-

TABLE 1
CLASSIFICATION OF
ESSENTIAL INFANTILE ESOTROPIA

Onset, birth to 6 months
Large angle, >30 prism diopters
Stable angle
Normal central nervous system
May be associated with
Defective abduction
Excessive adduction
Dysfunction of oblique muscles
Dissociated vertical deviation
Initial alternation with crossed fixation
Potential for normal binocular vision limited

TABLE 2
CHARACTERISTICS OF ESSENTIAL INFANTILE ESOTROPIA*
(N = 408)

CHARACTERISTIC	NO.	(%)
Amblyopia	144	(35)
Anomalous head posture	26	(6)
Dissociated vertical deviation (DVD)	208	(51)
Overaction of inferior obliques (OAIO)	277	(68)
DVD and OAIO (combined)	171	(42)
Manifest nystagmus	62	(15)
Manifest-latent nystagmus	41	(10)

*Mean deviation at distance, 44 △ (range, 5 to 100 △). Mean deviation at near, 49 △ (range, 10 to 95 △).

TABLE 3
DIFFERENTIAL DIAGNOSIS OF INFANTILE ESOTROPIA

Essential infantile esotropia
Sixth nerve palsy
Nystagmus dampening by convergence
Esotropia with central nervous system anomalies (Down's syndrome, albinism, cerebral palsy, mental retardation, and the like
Refractive accommodative esotropia
Sensory esotropia
Duane's syndrome type 1

cine, between 1973 and 1987. Only those patients were included in this study in whom the diagnosis of manifest esotropia was made before the age of 6 months by personal examination, by a referring ophthalmologist, or on the basis of at least three photographs taken at different times before the age of 6 months. Patients with associated neurologic disorders were excluded. The data are summarized in Table 2. The prevalence of associated findings such as amblyopia, dissociated vertical deviation, inferior oblique muscle dysfunction, and latent nystagmus is similar to that reported by most,[9] although not all,[10] previously published reports. The possibility exists that the association of infantile esotropia with dissociated vertical deviation or with manifest-latent or manifest congenital nystagmus[11-13] points toward subgroups with different pathophysiology and prognosis within the infantile esotropia syndrome. This prospect merits further investigation. Whenever possible it is necessary to make a clear distinction between essential infantile esotropia and other forms of esotropia occurring at birth or in infancy, since the prognosis of each of these conditions may differ.[8,14] The differential diagnosis of essential infantile esotropia has been discussed elsewhere[14] and is listed in Table 3.

Etiology

Little is known about the origin of essential infantile esotropia. Current concepts find their roots in two principal theories. The first, espoused by Worth, blames the squint on a defect of the fusion faculty putting the eyes into an "unstable equilibrium, ready to turn inwards or outwards on slight provocation."[15] Chavasse,[15] who was heavily influenced by the Pavlovian thinking of his time, rejected this theory by stating in his colorful prose that "we need no longer vainly gesticulate before the fireless altar of defect of the fusion faculty. . . ." Chavasse ignored the sensory side of fusion altogether. Fusion, he believed, was an overt motor response, acquired by usage. Chavasse felt that peripheral and central factors interfere with the development of binocular reflexes and thus cause squint.

These two opposing views have far-reaching therapeutic implications. If esotropia is caused by an inborn defect of the fusion faculty, no treatment, no matter how early in life, will restore normalcy. If, on the other hand, no such defect exists, a cure could be accomplished by aligning the eyes as early as possible. Indeed, it was Chavasse's thinking that triggered the era of early surgery that began with Costenbader. This school of thought dominates our current therapeutic practices, at least in the Western hemisphere.

Recent advances in infant psychophysics[16] have made it possible to add to these theories. This work has shown that certain vital sensory visual functions in the normal newborn are incompletely developed, including visual acuity, which is as low as 20/800 at birth[17]; contrast sensitivity[18,19]; monocular[20] and binocular retinal disparity sensitivity; and stereopsis.[21,22] To develop stable ocular alignment, a high-quality sensory input is required.[23] As this input is reduced during visual immaturity and, especially during the first three months of life, the infantile visual system may be vulnerable to

peripheral orbital-structural and innervational factors that may interfere with ocular alignment. This vulnerability could explain the frequent occurrence of transient intermittent or constant strabismus in the newborn.[3,4,24-27] At the age of 3 months, maturation of sensory functions begins, fusional vergences (motor fusion) are developing, and ocular alignment becomes stable. One could imagine that in certain infants, perhaps under the influence of genetic factors, certain peripheral physiologic or pathologic innervational influences override an innate capacity for normal binocular vision and cause esotropia. The exuberance of tonic convergence in childhood, a delayed maturation of fusional vergences, or anomalies in the brainstem neural integrators for vergence movement[28] are but a few of the many possible culprits to be considered in this interference. The validity of this hypothesis is testable with current methods of infant psychophysics.

Perhaps Chavasse was correct in assuming that children with infantile esotropia are not different from normals as far as their anlage for an intact fusion mechanism is concerned. It has been shown, for instance, that random dot stereopsis occurs transiently, even in esotropic infants after prismatic correction[29] or after surgical alignment.[30,31] These, as well as other, data[32] are at odds with the concept of a congenital absence of binocularity in infantile esotropia. The fact that bifoveal fusion and normal random dot stereopsis can never be attained in these patients does not contradict this theory. One could argue that surgical alignment even before the age of 1 year is too late to prevent deterioration of these functions.

Finally, we must ask whether animal experiments have helped us to better understand the pathophysiology of essential infantile esotropia. Such experiments are cited by the proponents of early surgery as they allegedly show an irreversible deterioration of binocular pathways in cats and monkeys with strabismus during infancy.[7,9,33] It is true that the so-called binocular cells in the striate cortex are permanently lost in infant monkeys after artificial strabismus.[34-36] However, these cells also disappear in nonstrabismic monkeys after eyelid suture[34,37] or after experimentally induced anisometropia.[38] Thus far the loss of binocularly innervated striate neurons has only been linked to an absence of stereopsis.[39,40] There is no evidence from animal research that binocular functions other than stereopsis, such as sensory and motor fusion, are similarly affected by abnormal visual experience early in life. There is currently no animal model for essential infantile esotropia.

Goals of Treatment

A cure of strabismus may be defined as a restoration of single binocular vision in the practical field of gaze, that is, orthotropia or asymptomatic heterophoria; normal visual acuity in each eye; normal stereoacuity on random dot testing; normal retinal correspondence; and stable sensory (bifoveal) and motor fusion. The noteworthy isolated case of Parks[41] notwithstanding, there is universal agreement between strabismologists that complete restoration of normal binocular vision with normal random dot stereopsis is unattainable in infantile esotropia. However, this conclusion need not lead to capitulation before a seemingly incurable anomaly in which surgery produces at best an improved cosmetic appearance. Stereopsis, while essential for certain occupations, is an epiphenomenon of binocular vision, rather than its highest form. Normal sensory and motor fusion also occurs in the absence of stereopsis.

A cure is not absolute, but may consist of several grades of subnormal or abnormal binocular cooperation.[2] We must ask: What is the nature of these subnormal or abnormal forms of binocular vision? Of what functional benefit are they for the patient? How often do they occur in a group of surgically treated patients with essential infantile esotropia? Does their occurrence depend on the age at which the eyes are surgically aligned?

Binocular Cooperation After Surgery

Erroneous interpretation of testing results and the unfortunate practice of lumping together normal and the different degrees of subnormal and abnormal binocular vision have made it difficult for the reader of contemporary ophthalmic literature to judge whether surgery, as claimed by many authors, must be performed before the age of 2 years to obtain a functionally useful result.[7,9,33,42] Precise information about the state of sensory and motor cooperation of the eyes cannot be gained by the stereotypical application of one or the other favorite tests, as there is no single test that yields all the answers. For reasons discussed elsewhere,[14] the presence of gross stereopsis, the visibility of the four dots on the Worth

TABLE 4
SUBNORMAL BINOCULAR VISION

Orthotropia or asymptomatic heterophoria
Normal visual acuity in both eyes
Fusional amplitudes
Normal retinal correspondence
Foveal suppression in one eye in binocular vision
Reduced or absent stereopsis
Stability of alignment
Optimal treatment result

four-dot test, a cross on the Bagolini striate glass test, or the results of the cover or cover-uncover tests, if taken as isolated findings, do not provide sufficient information about the normalcy and stability of binocular cooperation. These tests become significant only if correlated with each other and with additional tests not mentioned here. In 1984 I suggested classifying the results of surgery in infantile esotropia into the following categories: (1) subnormal binocular vision (Table 4), (2) microtropia (Table 5), (3) small angle and cosmetically acceptable residual esotropia or consecutive exotropia (Table 6), and (4) large angle residual esotropia or consecutive exotropia that requires additional surgery (Table 7). The tests required to diagnose these conditions were also described.[14] The following case reports illustrate the characteristic features of subnormal binocular vision, microtropia, and small angle esotropia.

Case 1

A constant esotropia was diagnosed in this 8-year-old girl at the age of 5 months by a pediatric ophthalmologist. Photographs supplied by the parents documented an esotropia on all pictures taken after the age of 3 months. The child was first examined at our institution at the age of 7 months. An esotropia of 30 prism diopters was present at near and distance fixation. The child preferred fixation with the left eye, but could hold fixation with the right eye over several blinks. A cycloplegic refraction showed emmetropia in each eye. The fundi were normal and nystagmus, anomalous head posture, or dysfunction of the oblique muscles were absent. At the age of 10 months, the right medial rectus muscle was recessed 5 mm and the right lateral rectus muscle was resected 8 mm. The patient was orthotropic for several weeks, but over a period of several months the eyes returned to their preoperative deviation of 30 prism diopters. At age 15 months, the left medial rectus muscle was recessed 4 mm and the lateral rectus muscle was resected 7 mm. The patient is now 8 years old and has an uncorrected visual acuity in each eye of 20/20 at distance. However, visual acuity of each eye is reduced to 20/60 when tested with the Vectograph test, indicating the presence of a foveal suppression scotoma that is present only under binocular conditions. The 4-prism diopter base-out prism test is positive for a foveal scotoma in the right eye. She has an esophoria of 10 prism diopters at near and distance, with rapid fusional recovery upon uncovering either eye. Convergence amplitudes as measured with a rotary prism are +12/+8 prism diopters at distance and +24/+18 prism diopters at near

TABLE 5
MICROTROPIA

Inconspicious shift or no shift on cover test
Mild amblyopia frequent
Fixation central or parafoveolar
Fusional amplitudes
Anomalous retinal correspondence
Reduced or absent stereopsis
Some stability of alignment
No further treatment except amblyopia prevention
Desirable treatment result

TABLE 6
SMALL ANGLE ESOTROPIA/EXOTROPIA (<20 △)

Cosmetically acceptable
80% have anomalous retinal correspondence
Less stability of angle
No further treatment except amblyopia prevention
Acceptable result

TABLE 7
LARGE ANGLE ESOTROPIA/EXOTROPIA (>20 △)

Usually cosmetically unacceptable
Less chance for anomalous retinal correspondence, suppression prevails
Unstable angle
Unacceptable result

fixation. She has only gross stereopsis on the Titmus fly test and no stereopsis on random dot testing. This patient has subnormal binocular vision and no further treatment is planned.

Case 2

This 9-year-old boy was examined in our clinic at age 3 months. The parents had noted that his eyes had turned in for several weeks. The patient could hold and maintain fixation with either eye and had a constant esotropia of 30 prism diopters at near fixation as determined with the Hirschberg test. Cycloplegic refraction showed a hypermetropia of R.E: +1.00 D sphere and L.E.: +1.75 D sphere. No nystagmus or anomalous head posture was noted. The fundi were normal. Reexamination several weeks later confirmed these findings. At the age of 4 months we recessed both medial recti 4 mm. One year later the esotropia had returned to its original angle and a V-pattern was present. Both lateral recti were resected 5 mm and transposed upward one muscle width. At the age of 3 years, the patient had again developed an esotropia of 30 prism diopters. A retroequatorial myopexy of both medial recti was performed 19 mm from the corneoscleral limbus. Postoperatively, the deviation has varied between 10 prism diopters of esotropia and 10 prism diopters of exotropia at near and distance fixation. On the last examination at the age of 9 years, the uncorrected visual acuity was 20/25 in each eye. The patient failed the TNO-random dot stereotest. The cover test showed an esodeviation of only 2 to 4 prism diopters. The afterimage and Bagolini tests were positive, indicating deep-seated anomalous retinal correspondence. This patient has a secondary microtropia and no further treatment is planned.

Case 3

This 7-year-old boy was noted by his mother to have an esotropia at the age of 6 months. However, inspection of photographs showed that an esotropia of the alternating fixation type had been present since the age of 3 months. The patient was first examined in our clinic at the age of 18 months. Prism cover testing showed an alternating esotropia of 35 prism diopters at near and distance fixation with overaction of both inferior oblique muscles and a moderate V-pattern. Cyclogyl refraction showed +0.75 D sphere in each eye. The fundi were normal, and nystagmus or an anomalous head posture was absent. At the age of 2 years, the child underwent a 4-mm recession of the left medial rectus muscle, a 6-mm resection of the left lateral rectus muscle, and a myectomy of both inferior oblique muscles. The patient has been reexamined at semiannual intervals for the past five years. His uncorrected visual acuity is R.E.: 20/25 and L.E.: 20/20. A residual esotropia of 18 prism diopters at near and 12 prism diopters at distance fixation has remained stable during the follow-up period. The afterimage and Bagolini tests were positive, indicating deep-seated anomalous retinal correspondence. The patient is stereoblind. The parents are pleased with a satisfactory cosmetic result. No further treatment is planned for this residual small angle esotropia.

It is not possible in each case to distinguish clearly between subnormal binocular vision and microtropia on the one hand or between microtropia and small angle esotropia on the other hand. A certain amount of overlap and variance exists that defies our attempts to force biologic phenomena into a rigid system of classification. Little is gained in our quest for knowledge, however, when clear distinction between these treatment results is possible but neglected, as is the case in many contemporary studies on the surgical outcome of infantile esotropia.

Functional Benefits of Anomalous Binocular Vision

Anomalous retinal correspondence occurs, as a rule, after surgical treatment of essential infantile esotropia in patients with microtropia[43,44] and in most patients with residual small angle esodeviations or exodeviations.[45] Thus, with the exception of patients with subnormal binocular vision in whom retinal correspondence is normal, anomalous retinal correspondence remains as a permanent residual sensory defect in most treated patients.

While there can be no question that the quality of binocular vision on the basis of normal retinal correspondence is superior to that obtained on the basis of anomalous correspondence, our thinking about anomalous correspondence has undergone drastic changes during the last 25 years. Prior to that time, many ophthalmologists and most orthoptists considered anomalous correspondence as a formidable obstacle to the restoration of normal binocular vision, to be treated with almost religious zeal by a variety of orthoptic training methods, including prisms. In my opinion, this treatment is futile in the case of the infantile

esotropic individual. Moreover, it may produce abysmal results in formerly asymptomatic patients who may acquire intractable diplopia from an ill-advised and irreversible elimination of a sensorial adaptation that had permitted comfortable binocular vision in the presence of a residual small angle deviation.

Currently we think of anomalous retinal correspondence as a functionally beneficial state of binocularity that should not be disturbed because it is superior to suppression. The visual input from a suppressed eye is limited and of no apparent benefit to binocular vision other than the elimination of diplopia. Conversely, anomalous correspondence provides the patient with a residual manifest strabismus with several functional benefits.[46] These include simultaneous binocular perception,[47] fusional vergences,[48,49] an intact binocular visual field, normal distance judgment,[50,51] and, in many instances, even gross stereopsis.[43,44,52] Treatment of this condition should be reserved for children with esotropia acquired at about the age of 3 or 4 years. In such patients anomalous correspondence indeed presents an obstacle to a complete cure.

Prevalence of Different Treatment Results

The results of surgical attempts to align the eyes as closely as possible to the orthotropic position by one or multiple operations were studied in 358 of our 408 patients with a documented onset before the sixth month of life in whom sufficient data and follow-up (mean, 39.4 months; range, one to 203 months) were available. Patients with neurologic disorders and acute dampening of a manifest congenital nystagmus by convergence[12,13] were excluded from this study. Surgical methods used included unilateral or bilateral recession/resection and, for the past three years, large (5 to 8 mm) bilateral recessions of the medial recti. Whenever indicated, surgery for dysfunction of the oblique muscles was performed in the same session. No attempt is made here to compare the effectiveness of one or the other of these procedures.

Of 358 patients, 71 (20%) achieved subnormal binocular vision (Fig. 1). Only three patients in this group had stereopsis on the Titmus test (one with 200 seconds of arc and two with 3,000 seconds of arc), and none had stereopsis when tested with random dots (TNO test). Twenty-five (7%) of the patients were microtropic and 140 (39%) had a residual, cosmetically insignificant esotropia or exotropia. A residual esotropia was three times more common than a residual exotropia. An esotropia and exotropia of more than 20 prism diopters remained in 70 (20%) and 52 (15%) patients, respectively, a result that we consider a therapeutic failure. Many patients in the latter two groups will require reoperation.

While these results are far from perfect, they are not nearly as dismal as one may conclude from older reports in the literature, especially since we have learned to consider anomalous retinal correspondence in a more favorable light. Some form of binocular cooperation, ranging from near normal (subnormal binocular vision) to anomalous (microtropia and small angle esotropia or exotropia) occurred in 236 (66%) of our patients. To the mother who asks "Will my child ever be able to use the eyes

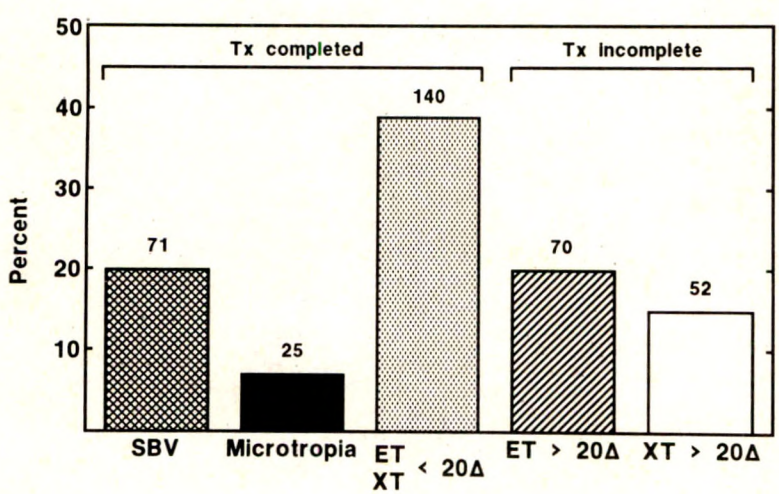


Fig. 1 (von Noorden). Surgical results in 358 patients with infantile esotropia. SBV, subnormal binocular vision; ET, esotropia; XT, exotropia; Tx, treatment.

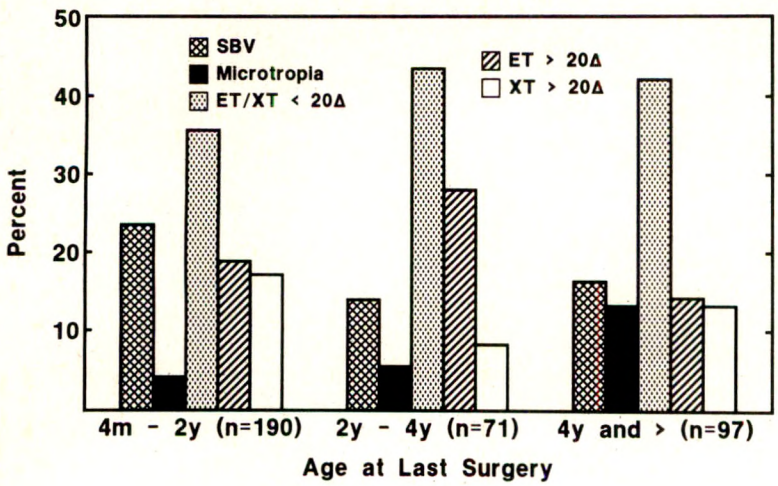


Fig. 2 (von Noorden). Prevalence of functional state in 358 patients according to age at alignment. SBV, subnormal binocular vision; ET, esotropia; XT, exotropia.

together after surgery?" we can answer, "Yes, there is a very good chance, although complete normalcy cannot be expected."

Age at Alignment and Results

Finally, we must ask whether the quality of surgical results in terms of optimal (subnormal binocular vision), desirable (microtropia), acceptable (small angle esotropia or exotropia), or unacceptable (large angle residual esotropia or consecutive exotropia) outcomes depends on the age at which surgical treatment is completed, that is, when the eyes have been aligned by one or several operations as close to the orthotropic position as possible. The prevalence of the various functional end stages of therapy grouped according to whether therapy was completed between 4 months and 2 years, 2 to 4 years, or older than 4 years are shown in Figure 2. These data were subjected to multinomial logistic regression analysis to estimate the effect of the age at alignment on the relative probabilities of the five end stages of therapy. This analysis showed that as age at completion of surgical therapy increased, the probability of an optimal outcome (subnormal binocular vision) decreased ($P = .02$). Increasing age at the completion of treatment tended to move the patients away from subnormal binocular vision and into the less desirable microtropia and small angle esotropia or exotropia groups.

These data, although based on evaluation criteria quite different from those used by previous investigators, are in accordance with the current view that surgery completed before the age of 2 years yields superior results.[33,42,53,54] However, they are at variance with the admonition that unless surgery is completed before that time, a functionally useful form of binocular vision cannot be expected.[7] In fact, many of our patients achieved such results when surgical treatment was concluded after the age of 2 or even 4 years.

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OPHTHALMIC MINIATURE

He fished in his pocket for his two pairs of sunglasses. In the same pocket he felt a hard, smooth, unidentified lump of very heavy metal. He pulled it out and looked at it. He blinked at it in surprise. Where had he got that? He returned it to his pocket and put on the sunglasses, annoyed to discover that the metal object had scratched one of the lenses. Nevertheless, he felt much more comfortable with them on. They were a double pair of Joo Janta 200 Super-Chromatic Peril Sensitive Sunglasses, which had been specially designed to help people develop a relaxed attitude to danger. At the first hint of trouble they turn totally black and thus prevent you from seeing anything that might alarm you.

Douglas Adams, *The Restaurant at the End of the Universe*
Pocket Books, 1980, p. 35

Juxtapapillary Choroidal Neovascularization in Older Patients

Jane C. Kies, M.D., and Alan C. Bird, M.D.

We studied retrospectively 55 eyes with juxtapapillary choroidal neovascularization in 42 patients over the age of 50 years. In all but four lesions, the choroidal neovascularization was undetected, causing the choroidal new vessel complexes to be ill defined, discontinuous, and show irregular dye leakage on fluorescein angiography. Growth of the lesion was unpredictable. Visual loss occurred in eight of 16 eyes during the first six months of follow-up. Recurrent neovascularization after photocoagulation originated in some patients from outside the pretreatment subretinal complex. Of the 15 patients with bilateral involvement, 13 had juxtapapillary lesions. Fellow eyes in patients with unilateral juxtapapillary lesions showed no predisposing abnormality at or near the nerve head. The prevalence, density, and fluorescein angiographic characteristics of drusen were different from those in age- and sex-matched patients with macular neovascularization.

JUXTAPAPILLARY SUBRETINAL neovascularization in younger patients may occur in response to conditions such as optic disk drusen,[1] optic nerve pits,[2] optic disk edema,[3,4] myopia,[5] angioid streaks,[6] presumed ocular histoplasmosis syndrome,[7,8] trauma,[9] uveitis, serpiginous choroidopathy,[10] and infiltrative optic nerve lesions.[11] No such association has been established in older patients. The function and development of these lesions is not well understood, and it is unknown whether or not they are part of the spectrum of age-related macular disease.

We reviewed retrospectively the available records of patients with juxtapapillary choroidal neovascularization who had been examined at our institution. The goal of the initial part of this study was to gain more information concerning the clinical appearance and pattern of such lesions. Subsequently, we sought to identify whether or not juxtapapillary choroidal neovascularization is part of the spectrum of age-related macular disease. We compared the clinical appearance and angiographic characteristics of the fellow eye in patients with juxtapapillary choroidal neovascularization to age- and sex-matched patients with perifoveal (macular) neovascularization.

Patients and Methods

We identified 42 cases of juxtapapillary choroidal neovascularization in patients over the age of 50 years from the 70 cases identified between 1970 and 1986 at our institution. None of the 42 patients had optic disk drusen, optic nerve pits, angioid streaks, serpiginous choroiditis, uveitis, presumed ocular histoplasmosis syndrome, optic neuritis, papilledema, sarcoidosis, severe myopia, or optic nerve nevi. The mean age of the 42 patients was 68.5 years; there were 29 women aged 50 to 83 years (mean, 68 years) and 13 men aged 60 to 76 years (mean, 66 years). Patients were asked to return for further clinical examination. In 13 patients, bilateral juxtapapillary neovascularization was detected at the first examination or developed during the follow-up period. Of the 55 eyes, 13 underwent one or more sessions of photocoagulation.

The clinical records were reviewed for the nature and duration of the patients' symptoms, visual acuity, and details of the clinical exami-

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nation. We verified that the subretinal new vessels were adjacent to the disk in each lesion by clinical examination where possible and stereoscopic color fundus photography and fluorescein angiography.

Laser treatment was performed when the choroidal neovascularization was believed to be an immediate threat to the fovea. The decision to treat was somewhat arbitrary, but was made in patients who were symptomatic, whose symptoms were progressing, and in whom the subretinal new vessels were more than 200 μm from the fovea. Photocoagulation was intense and confluent, covering all neovascular tissue in the macula. It did not cover the margin of the disk. Neovascular tissue outside the vascular arcades was not treated since it was not considered a threat to the fovea. Laser treatment consisted of argon blue-green wavelengths, except where large retinal vessels prevented adequate delivery of energy to the subretinal tissues. In such cases the red energy of the krypton laser was used. Argon blue-green was used in seven cases and krypton in six. The patients were examined two, four, and eight weeks after treatment, and, generally, every three months thereafter unless further photocoagulation was required. The follow-up period was 12 months or more in all treated patients (mean, 28 months).

In order to determine the relationship of juxtapapillary choroidal neovascularization to age-related macular disease, the appearance and outcome of the fellow eyes in the study patients were documented. Both eyes were examined in the 15 patients who had or developed bilateral neovascularization to identify its location and incidence. If a high risk of developing bilateral disease were found, it would imply that the fellow eye might show abnormalities that predispose to such lesions. Precipitating causes were sought by examining the optic disk and juxtapapillary retina in the fellow eye of the 29 patients with unilateral juxtapapillary neovascularization for papillary, peripapillary, or macular abnormalities.

The extent and nature of age-related changes at the level of Bruch's membrane and the pigment epithelium were studied. Eyes in which the central 1,600 μm of the macula could not be fully examined because of poor photographic and angiographic documentation or the presence of an obscuring lesion were excluded. A total of 40 eyes were eligible from both the fellow eyes of study patients and eyes with a juxtapapillary new vessel complex restricted to the peripapillary area. If present, the drusen were measured for size, distribution, and density using a standardized grid,[12,13] and fluorescence characteristics on early and late fluorescein angiogram frames were recorded. An identical analysis was undertaken of the fellow eyes of an age- and sex-matched control group of patients with macular subretinal neovascularization. Each patient with drusen in the study group was age- and sex-matched to a patient in the control group. Only fundus photographs from the initial examination were used so that any differences could not be ascribed to the different duration of known disease in the two groups. The mean age of the two groups was 72 years, and each group comprised 15 women and nine men.

Results

Visual results—In 49 of 55 eyes the presence of juxtapapillary choroidal neovascularization caused blurring and distortion of vision, altered color perception, scotomas, and floaters. These symptoms lasted for a few days to several months, and some patients reported poor vision in the affected eye for several years. In 40 of 55 eyes the symptoms could be attributed to either subretinal fluid, hemorrhage, or exudate derived from the neovascular tissue without clearly identifiable subfoveal extension of a new vessel complex. In the remaining eyes poor vision could be attributed to subfoveal new vessels. Patients with poor visual acuity at the time of the initial examination (20/80 or worse) had no functional recovery of vision after a minimum follow-up period of six months (mean, 26.4 months). In 24 eyes initial visual acuity was 20/40 or better (Table 1). Of these 24 eyes, 16 were followed up for six months or more: eight maintained a visual acuity of 20/40 or better at six months, and five maintained that level at one year. Of these five eyes, three lost two or more lines of vision after one year because of renewed growth of the juxtapapillary new vessels, one had good visual acuity (20/40) at four years, and the remaining patient was lost to follow-up. Two patients had a nasally located juxtapapillary lesion in one eye, but both retained a visual acuity of 20/40 or better at six and 12 months.

Fundus changes—In 43 of 55 eyes the choroidal neovascular complex was contiguous with 180 degrees or more of the disk circumference.

TABLE 1
VISUAL ACUITY DURING FOLLOW-UP PERIOD

VISUAL ACUITY	INITIAL EXAMINATION (NO. OF EYES)	FOLLOW-UP PERIOD (NO. OF EYES) 1–3 MOS	3–6 MOS	6–12 MOS	>12 MOS	≥18 MOS	≥4 YRS
20/20	10	6	5	3	2	0	0
20/30	12	10	10	4	2	2	1
20/40	2	1	1	2	1	1	1
20/60	8	6	4	3	2	1	0
20/80	5	3	2	1	1	0	0
20/120	1	0	1	0	0	0	0
20/200	11	11	9	9	6	7	4

In six eyes the complex completely surrounded the optic nerve head. These large lesions were all characterized by elevation of the retina, hemorrhage, or exudate. In ten eyes less than one half the circumference of the temporal disk margin was adjacent to choroidal neovascular tissue. In the remaining two eyes the choroidal neovascular tissue was located adjacent to less than half of the nasal circumference of the disk. These appeared as ill-defined gray patches of slightly elevated subretinal tissue.

Fluorescein angiography showed the new vessel complex clearly throughout the lesion in only four eyes. Most cases (51 of 55 new vessel complexes) showed heterogeneous hyperfluorescence with islands of neovascular tissue filling slowly and irregularly after the choriocapillaris. The lesions had an ill-defined edge and irregular late hyperfluorescence. Small points of hyperfluorescence were often seen beyond the boundary of the main choroidal new vessel complex (Figs. 1 and 2). The juxtapapillary portion of the new vessel system lost its capillary content over time, allowing the retina to flatten onto atrophic choroid or scar tissue. At this time, easily identifiable subretinal neovascularization appeared near the fovea, with pigment epithelial and choroidal atrophy between the new vessels and the disk. The only indication of the origin of the lesion was underlying feeder vessels passing from the peripapillary choroid to the subretinal neovascular complex at the fovea.

Response to treatment—In seven of 13 treated lesions the new choroidal vessels were successfully closed. They did not reappear during the follow-up period, which ranged from 27 to 84 months. Of these seven lesions, three required only one treatment session; visual acuity in these eyes remained 20/30 or better (Fig. 3). The remaining four lesions required further treatment within three months of the initial photocoagulation for recurrent new vessels at the foveal edge or within the area of the initial

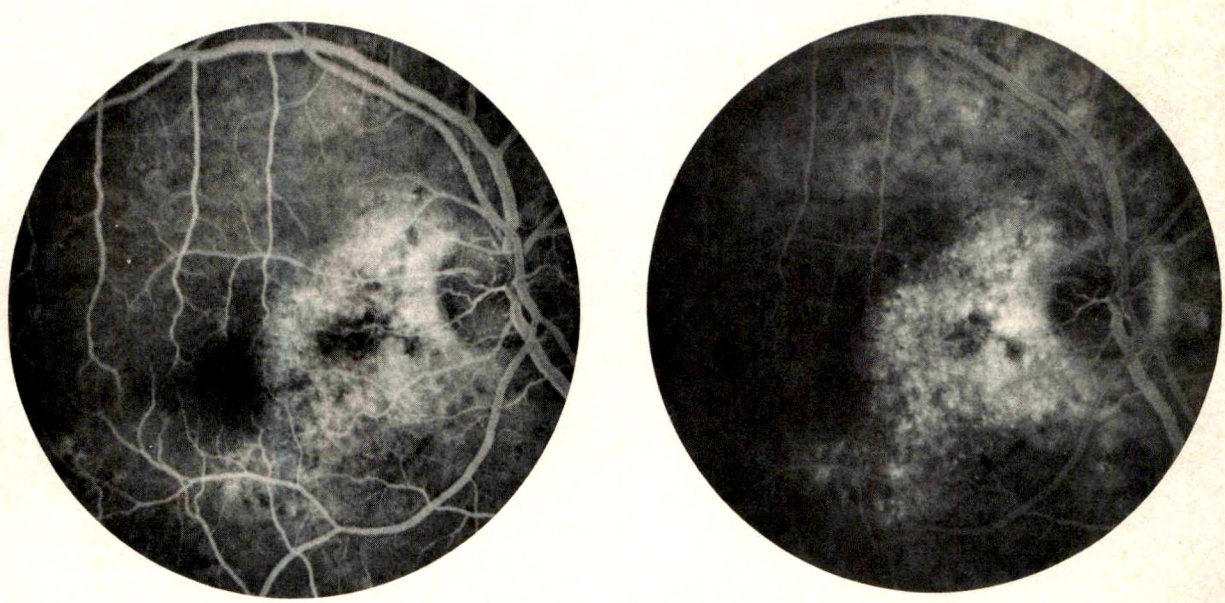


Fig. 1 (Kies and Bird). Fluorescein angiograms in the left eye of a 63-year-old man who experienced distortion for several weeks. Visual acuity was 20/30. Subretinal new vessels were visible in one area during dye transit (left), with minimal leakage in the late phase (right).

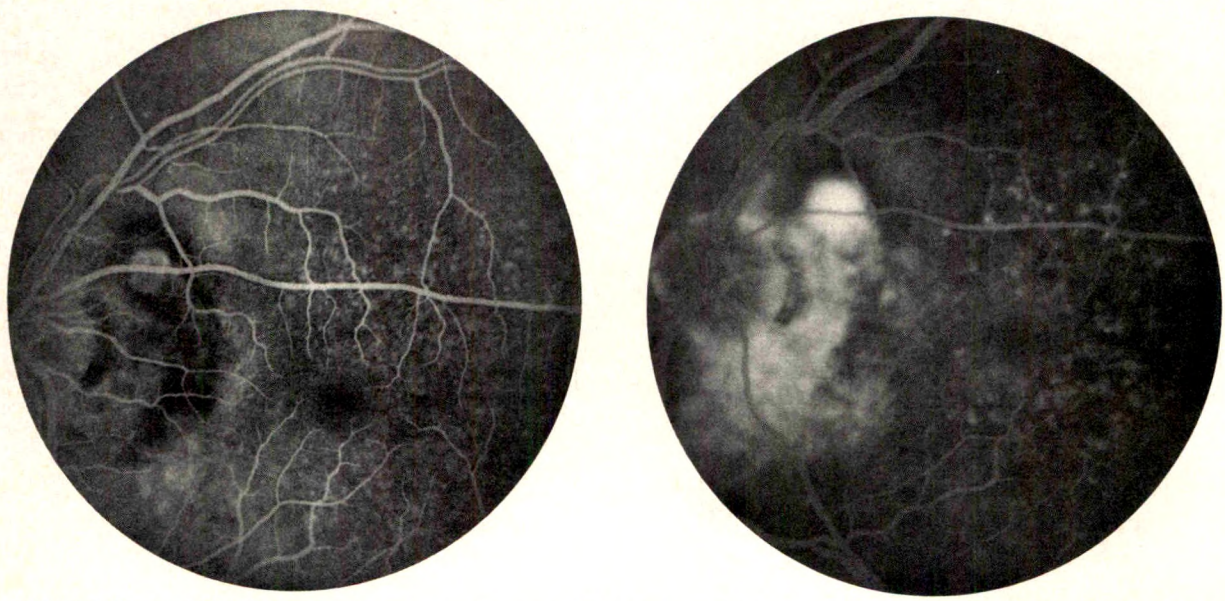


Fig. 2 (Kies and Bird). Fluorescein angiograms in the left eye of a 65-year-old woman who maintained a visual acuity of 20/20 in this eye for 19 months. Left, Venous laminar phase and right, late stage. Note mixed undetected and manifest choroidal neovascularization. New vessels are easily seen in the upper part of the lesion.

laser scar. Visual acuity remained 20/30 12 months after treatment in two eyes and 20/20 after 18 months in two eyes.

In the remaining six treated lesions the neovascular tissue extended to a subfoveal site. In three lesions the recurrence developed in the bed of the existing laser scar, with one lesion having subfoveal neovascular tissue supplied by long feeder vessels originating near the nerve head (Fig. 4). In the other three lesions renewed subretinal vascular proliferation recurred within six weeks of the treatment from outside the treatment area, at a site in which no abnormality was visible on the original angiogram (Fig. 5).

Predisposing factors—Of the 15 patients who had new subretinal vessels in the fellow eye at the time of the initial examination or who developed them during the follow-up period, 13 (87%) had a juxtapapillary lesion in the second eye and only two (13%) had a primary parafoveal lesion.

In the fellow eyes of the patients with juxtapapillary choroidal neovascularization, the optic disks did not appear different from those in the age- and sex-matched macular neovascularization control group. There was only mild physiologic cupping, with no obvious disk drusen. Most patients in both groups showed pigment epithelial changes around the nerve, consisting of pigment epithelial depigmentation, with marginal hyperpigmentation temporal to the margin of the disk in some patients. These changes were similar in the two groups. Only one patient with a juxtapapillary lesion in one eye had a larger area of atrophy in the fellow eye; the atrophy covered an area measuring one-quarter disk diameter, which increased in fluorescence during the angiogram but demonstrated no new vessels.

Of the 40 eyes in patients with juxtapapillary choroidal neovascularization in which the macular region was easily visualized, 16 had no clinical or photographic evidence of drusen. Conversely, all 40 patients with macular choroidal neovascularization had evidence of drusen in the fellow eye. This difference was statistically significant ($P < .001$). In the 24 study patients with drusen, the changes at the level of Bruch's membrane differed from those in the control group. The drusen in the patients with juxtapapillary lesions were less dense ($P < .05$) and tended to have brighter fluorescence in the late stage of the angiogram ($P < .05$) than the drusen in patients with macular choroidal neovascularization. The size of the drusen and their appearance in the early phase angiograms did not differ between the two groups (Table 2).

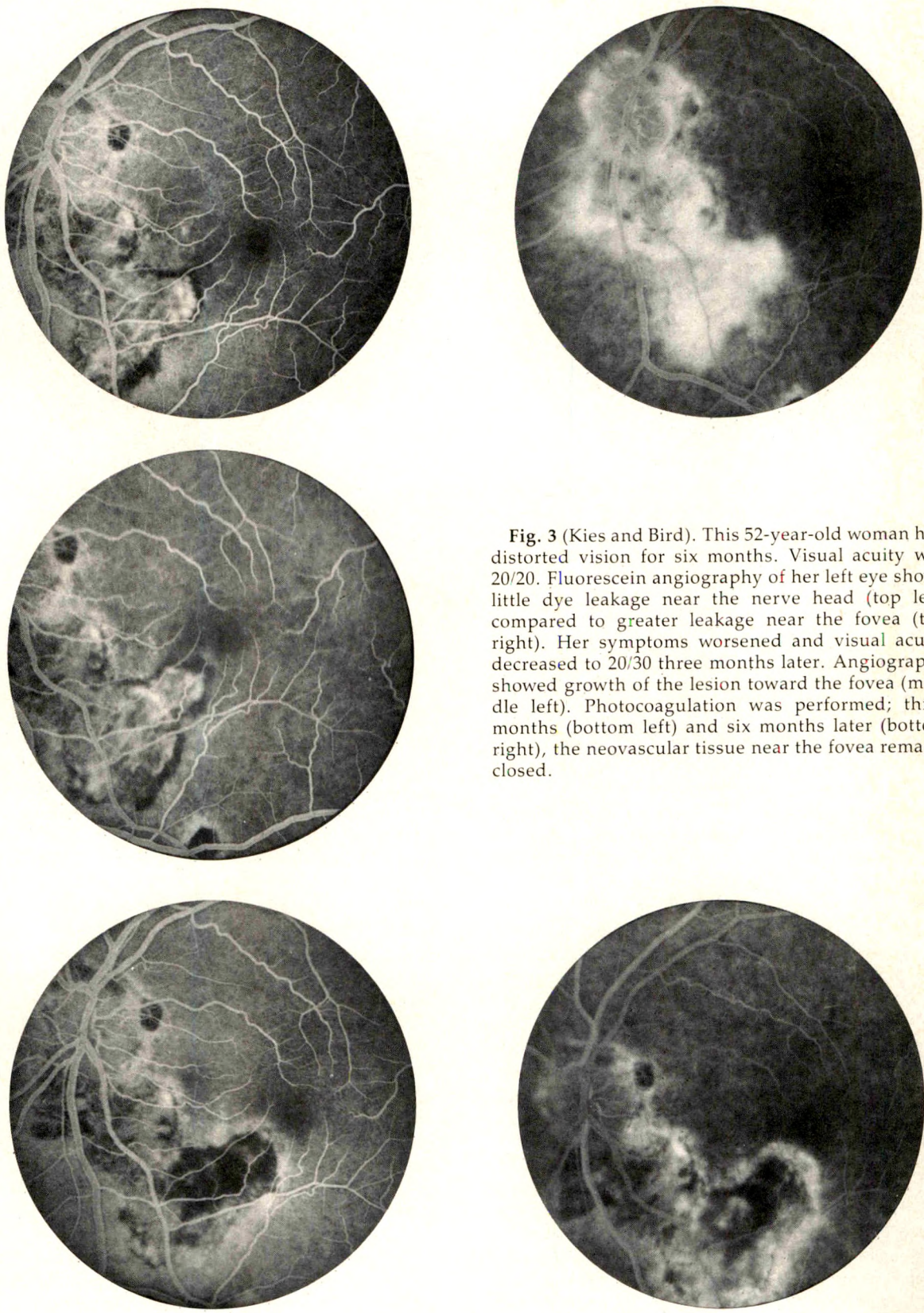


Fig. 3 (Kies and Bird). This 52-year-old woman had distorted vision for six months. Visual acuity was 20/20. Fluorescein angiography of her left eye shows little dye leakage near the nerve head (top left) compared to greater leakage near the fovea (top right). Her symptoms worsened and visual acuity decreased to 20/30 three months later. Angiography showed growth of the lesion toward the fovea (middle left). Photocoagulation was performed; three months (bottom left) and six months later (bottom right), the neovascular tissue near the fovea remains closed.

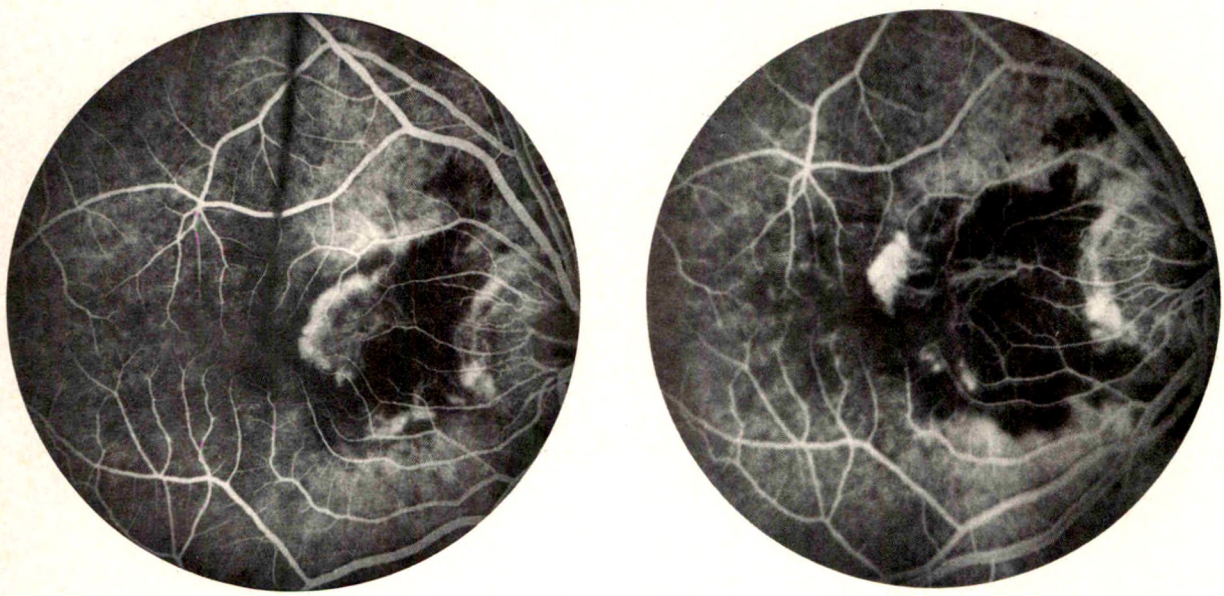


Fig. 4 (Kies and Bird). Fluorescein angiography in a 62-year-old woman with recurrence after the first (left) and the second photocoagulation (right) demonstrates feeder vessels originating in the juxtapapillary choroid, supplying capillaries at the fovea.

Discussion

Most lesions seen in this study had the characteristics of occult neovascularization. The neovascular tissue was not well demonstrated by fluorescein angiography, the vascular detail was not clearly shown, dye leakage was irregular, and the margins of the new vessel complex were poorly defined. Such new vessel complexes are believed to grow on the inner surface of Bruch's membrane and are covered by a layer of normal retinal pigment epithelium. The pigment epithelium would be expected to modify the appearance of the lesion because of the presence of a pigmented layer between the vessels and the observer. Miller, Miller, and Ryan[14] also found that the retinal pigment epithelium may modify the pattern of the new vessel system. They found that the evolution of subretinal new vessels that developed as a result of high energy density photocoagulation in rhesus monkeys was determined by the response of the pigment epithelium. In some lesions the new vessel complex was completely covered on its inner surface by proliferating pigment epithelium. In these lesions the blood vessels stopped growing, did not leak plasma constituents, and could not be detected by fluorescein angiography. Conversely, the new vessels that proliferated beneath the receptors grew rapidly and leaked profusely on angiography. The mechanisms by which retinal pigment epithelium may influence blood growth have been illustrated by Glaser and associates.[15] There is circumstantial evidence of this process in humans. Widespread subpigment epithelial neovascularization in eyes in which new vessels were not well demonstrated on fluorescein angiography, albeit some months earlier, has been demonstrated histopathologically.[16-18]

The discontinuous hyperfluorescence we described in these lesions may be derived from a single new vessel complex of which part was not seen, either because it was obscured or because it did not leak fluorescein. This would occur if the influence of the retinal pigment epithelium varied from one area to another in a single neovascular complex. Similarly, the spots of hyperfluorescence seen beyond the edge of the visible lesion may be capillary tufts extending from the edge of a large lesion, rather than some benign change at the level of Bruch's membrane.

The presence of occult neovascularization determined the appearance of the lesion and its evolution. The growth of the lesion was slow

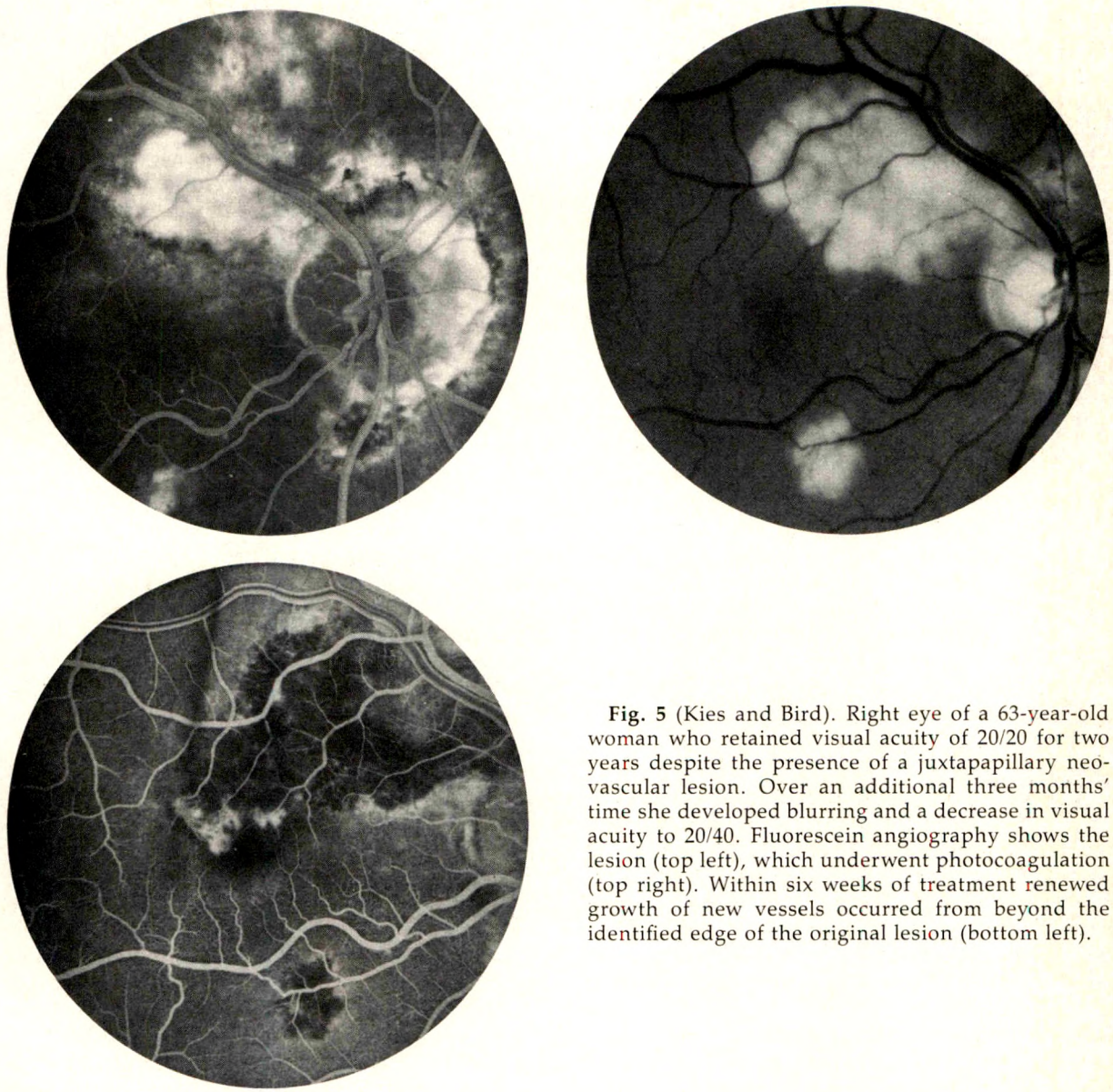


Fig. 5 (Kies and Bird). Right eye of a 63-year-old woman who retained visual acuity of 20/20 for two years despite the presence of a juxtapapillary neovascular lesion. Over an additional three months' time she developed blurring and a decrease in visual acuity to 20/40. Fluorescein angiography shows the lesion (top left), which underwent photocoagulation (top right). Within six weeks of treatment renewed growth of new vessels occurred from beyond the identified edge of the original lesion (bottom left).

and unpredictable. This accounts for the preservation of good visual acuity for over one year in some patients with juxtapapillary choroidal neovascularization as compared to the visual outcome in patients with macular choroidal neovascularization.[19,20] However, renewed growth of the subretinal new vessels was recorded after many months of mild symptoms and good vision. This second growth phase must be caused by some change in the determinants of vessel growth, such as ingress of macrophages or alteration of the influence of the retinal pigment epithelium. In foveal lesions in the elderly there is usually only a single growth phase.

During the second growth phase, a lesion with rapidly growing parafoveolar new vessels originated from an old juxtapapillary lesion. The atrophy of the nasal portion of such a lesion would have made it difficult to identify the true nature of the original lesion unless it had been previously identified.

The unpredictable evolution of the lesions made the indications for photocoagulation treatment unclear. Furthermore, the angiographic appearance of the occult neovascular

TABLE 2
CHARACTERISTICS OF DRUSEN IN FELLOW EYES
(N = 24)

PATIENTS	SIZE (μM)			DENSITY (μM APART)			FLUORESCEIN ANGIOGRAPHIC FINDINGS*					
							EARLY PHASE			LATE PHASE		
	0–50	50–500	>500	>200	<200	0	0	1	2	0	1	2
Patients with juxtapapillary choroidal neovascularization	4	19	1	20	4	0	4	8	12	3	3	18
Patients with macular choroidal neovascularization	3	18	3	4	15	5	7	8	9	6	8	10

*Fluorescence scale: 0, indistinguishable from choroid; 1, minimally brighter than choroid; and 2, brightly fluorescent.

tissue posed potential difficulties in performing adequate treatment. Once it was determined that the fovea was threatened, the area occupied by new vessels was difficult to outline because of the ill-defined edges of neovascularization, the apparent discontinuity of the neovascular tissue, and uncertainty as to the significance of the small points of hyperfluorescence beyond the margins of continuous hyperfluorescence. In three patients, recurrent neovascularization was detected within six weeks of the photocoagulation; it developed at a site that was clearly beyond the edge of angiographic change in the pretreatment angiogram. The recurrent vessels may have been part of an extension of the original lesion that were not seen because they were beneath normal retinal pigment epithelium. If this interpretation is correct, the photocoagulation technique should be modified. If possible, a wide margin of normal-appearing fundus should be treated around the lesion. Any angiographic abnormality around the edge of the lesion should be considered as potential extensions of the new vessel complex.

Most of the lesions were large before patients noticed any symptoms. Size also has an influence on therapy, and may account for recurrence from within the lesion, which is unusual in the smaller primary macular lesions. Laser photocoagulation may only affect the inner surface of the vascular complex, so that the large vessels in the depths of the lesions might remain perfused.

The high prevalence of occult neovascularization does not imply a disorder that is fundamentally different in its pathogenesis from macular choroidal neovascularization. Occult new vessels are being recognized more commonly in macular disciform lesions as a manifestation of age-related disease. The difference between macular and juxtapapillary disease is quantitative rather than qualitative. The identified high risk of a patient suffering the same fate in both eyes suggests that the origin of the new vessels is not determined by chance alone. We sought evidence of predisposing disease at the nerve head or in the peripapillary fundus in the fellow eyes of those patients with juxtapapillary new vessels. There appears to be a high risk of a similar lesion occurring in the same location in the second eye. No clinical manifestation of predisposing changes was identified.

We then recorded the age-related changes at the level of Bruch's membrane. The symmetry of such changes between fellow eyes has been well documented,[21,22] and it is reasonable to assume that the drusen in one eye would reflect the nature of the drusen in the fellow eye before new vessel growth. Changes in Bruch's membrane in the fellow eyes of patients with juxtapapillary new vessels appeared different from changes in the control group with respect to their prevalence, density, and angiographic characteristics.

Our observations show that if juxtapapillary choroidal neovascularization is a complication of age-related subretinal disease, it is distinct from primary macular disciform lesions. The pathogenesis in these two forms of disease may be different, and the pattern of juxtapapillary choroidal neovascularization necessitates a different therapeutic regimen than that used in macular choroidal neovascularization.

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OPHTHALMIC MINIATURE

The sun was available to the instrument he held. There was in his hands a give-and-take fragility, a balancement of objects seen, a relation between them that could be controlled: controlled by the eye, the fingers, and the slants and angles of glasses: mirrors: lenses. He longed for whatever revelations he might be holding to his forhead: for the sun, for something in the sky, or beyond the sky, to appear there, among the long heartless flashes of his blindness. Behind the dark, he thought, his neck muscles stiffening against his collar: beyond it: beyond.

James Dickey, *Alnilam*
Garden City, Doubleday & Company, Inc., 1987, p. 444

Role of the Vitreous in Branch Retinal Vein Occlusion

Masanori Kado, M.D., and Clement L. Trempe, M.D.

We analyzed the vitreous findings in 62 patients (62 eyes) with major branch retinal vein occlusion to determine whether vitreous examination was useful in predicting the development of retinal or disk neovascularization, or both. In 18 eyes with no or partial posterior vitreous detachment and large areas of capillary nonperfusion (5 disk diameters or more), ten eyes (55.6%) eventually developed neovascularization. Only three of the remaining 44 eyes (6.8%) developed neovascularization. The probability of this development was greater in eyes with no or partial posterior vitreous detachment at the initial vitreous examination (P = .0177, Cox's regression analysis), and in those with large areas of nonperfusion (P = .0097, Cox's regression analysis).

RETINAL OR DISK neovascularization, or both, are serious complications secondary to branch retinal vein occlusion.[1] Despite the hypothesis that angiogenic factors released by a hypoxic retina stimulate neovascularization,[2] its development is still difficult to predict in clinical practice. We studied the usefulness of vitreous examination combined with evaluation of nonperfusion on fluorescein angiography to predict the development of neovascularization.

Patients and Methods

We reviewed the records of 204 patients (212 eyes) with major branch retinal vein occlusion on or outside of the major vascular arcade. The patients had been examined using the El Bayadi-Kajiura preset lens between 1979 and 1986 at the Retina Associates. We selected 62 eyes (62 patients) that met the following criteria: (1) no neovascularization at first vitreous examination; (2) an area of retinal involvement of at least 5 disk diameters; (3) a period of 24 months or less from the onset of branch retinal vein occlusion to the first vitreous examination; (4) a period of at least six months from the first vitreous examination to the last visit; (5) fundus fluorescein angiography performed at least once; (6) no history of prophylactic scatter laser photocoagulation (eyes that had scatter laser photocoagulation or focal laser photocoagulation of the new vessels after developing neovascularization and macular photocoagulation for treatment of macular edema were included in this study); (7) absence of diabetic retinopathy; and (8) no surgery or other intraocular disease that might influence the development of neovascularization.

If both eyes of a patient met these criteria, the one that developed branch retinal vein occlusion first was selected for the study. One eye was excluded from the analysis because cataract prevented adequate visualization of the vitreous.

Follow-up examination, including measurement of corrected visual acuity, applanation tonometry, biomicroscopic examination of the anterior segment, indirect ophthalmoscopy, and fundus color photography, was done at about four-month intervals. Fundus fluorescein angiography was performed yearly to assess the extent of retinopathy and nonperfusion and the presence of neovascularization. Nonperfusion was defined as an area of 5 disk diameters or more of capillary nonperfusion. Vitreous examination was performed using an El Bayadi-Kajiura lens mounted on a photo-slit lamp. The vitreous condition was classified as no, partial, or complete posterior vitreous detachment, based on the position of the posterior vitreous cortex relative to the retina posterior to the equator.

The eyes were assigned to one of four groups according to the presence of nonperfusion and the vitreous condition. Group 1 comprised 20 eyes with perfused retina and vitreous attached to the retina (18 eyes had no posterior vitreous detachment; two eyes had partial posterior vit-

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reous detachment). Group 2 comprised 13 eyes with perfused retina and complete posterior vitreous detachment. Group 3 comprised 18 eyes with nonperfused retina and vitreous attached to the retina (17 eyes had no posterior vitreous detachment and one eye had partial posterior vitreous detachment). Group 4 comprised 11 eyes with nonperfused retina and complete posterior vitreous detachment.

Data storage, tabulation, and statistical analyses were performed using a personal computer.

Results

We studied the vitreous findings in 62 eyes (62 patients) (Table 1). Of the 18 eyes in Group 3, ten (55.6%) developed retinal neovascularization during the follow-up period (Table 2). However, only two (10%) of the 20 eyes in Group 1, none of the eyes in Group 2, and one (9.1%) of the 11 eyes in Group 4 developed retinal neovascularization during the follow-up period. Of the three eyes with partial posterior vitreous detachment, one with a nonperfused retina developed neovascularization from the retina to which vitreous was still attached, and two eyes did not develop neovascularization. One eye in Group 4 developed neovascularization from the peripheral retina near the vitreous base where vitreous might be attached to the retina.

TABLE 1
BASELINE DATA OF 62 PATIENTS WITH BRANCH RETINAL VEIN OCCLUSION

	NO.	(%)
Age at onset, range (yrs)	63.1 ± 17.9 (45–80)	—
Sex		
Men	38	(61.3)
Women	24	(38.7)
Initial visual acuity		
≤20/100	25	(40.3)
≥20/70	37	(59.7)
Nonperfusion		
<5 disk diameters	33	(53.2)
≥5 disk diameters	29	(46.8)
Initial condition of vitreous		
No posterior vitreous detachment	35	(56.5)
Partial posterior vitreous detachment	3	(4.8)
Complete posterior vitreous detachment	24	(38.7)
Time from onset to first vitreous examination, range (mos)	7.2 ± 7.0 (0–24)	—
Time from first vitreous examination to last visit, range (mos)	35.4 ± 22.2 (6–97)	—

TABLE 2
EYES WITH NEOVASCULARIZATION BY GROUP

	NO OR PARTIAL POSTERIOR VITREOUS DETACHMENT		COMPLETE POSTERIOR VITREOUS DETACHMENT		TOTAL	
	NO./TOTAL	(%)	NO./TOTAL	(%)	NO./TOTAL	(%)
Perfused	2/20 (Group 1)	(10.0)	0/13 (Group 2)	(0.0)	2/33	(6.1)
Nonperfused	10/18 (Group 3)	(55.6)	1/11 (Group 4)	(9.1)	11/29	(37.9)
Total	12/38	(31.6)	1/24	(4.2)	13/62	(21.0)

A Kaplan-Meier plot (Figure) shows the cumulative proportion of eyes that developed neovascularization in the four groups. In this plot, time was measured from the date of the first vitreous examination in each patient. The probability estimate of developing neovascularization by three years from the first vitreous examination was 0% in Groups 2 and 4, 5% in Group 1, and 63% in Group 3. There was no significant difference in the length of follow-up among the groups from the time of the initial vitreous examination to the last visit (Group 1, 35.5 ± 23.4 months; Group 2, 31.0 ± 24.5 months; Group 3, 37.5 ± 18.4 months; Group 4, 36.8 ± 25.1 months) ($F = .23$, $P = .874$ by analysis of variance).

Cox's regression analysis was used for statistical comparison of the risk factors that influence the development of neovascularization. The response variable was the development of neovascularization. Trial time extended from the date of the first vitreous examination to the date of the development of neovascularization or, if neovascularization did not develop, to the date of the last visit. The covariables in this model were age at onset, sex, visual acuity at first visit, nonperfusion, time period from the onset of branch retinal vein occlusion to the first vitreous examination, and vitreous condition at the first vitreous examination. Only nonperfusion ($P = .0097$) and vitreous condi-

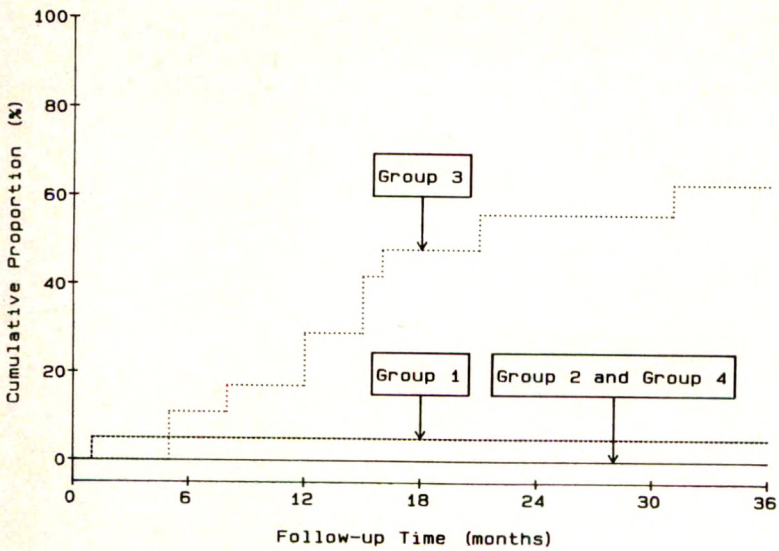


Figure (Kado and Trempe). Kaplan-Meier plot showing cumulative percentage of eyes with branch retinal vein occlusion that developed retinal or disk neovascularization, or both, in each group. Time was measured from the date of the first vitreous examination in each patient. Group 1, perfused retina and vitreous attached to the retina; Group 2, perfused retina and complete posterior vitreous detachment; Group 3, nonperfused retina and vitreous attached to the retina; Group 4, nonperfused retina and complete posterior vitreous detachment.

tion (P = .0177) affected development of neovascularization.

Of the 13 eyes that developed neovascularization, 12 had a follow-up vitreous examination (Table 3). One eye had complete posterior vitreous detachment at initial examination, and no follow-up vitreous examination was performed. The mean follow-up period from the first to the last vitreous examination was 36.9 months (range, 16 to 72 months). When neovascularization was first detected, there was no posterior vitreous detachment in nine eyes, partial detachment in three eyes, and complete detachment in one eye. Of the three eyes with partial posterior vitreous detachment, we could observe only one eye that developed neovascularization after partial posterior vitreous detachment developed. The vitreous condition in another two eyes was unknown when neovascularization occurred, because there was no posterior vitreous detachment before the development of neovascularization, and partial posterior vitreous detachment was found at the time neovascularization was first discovered. Therefore, the vitreous condition when neovascularization developed was no posterior vitreous detachment in nine eyes, partial detachment in one eye, complete detachment in one eye, and unknown in two eyes. Among the nine eyes that had no posterior vitreous detachment when neovascularization developed, three later developed partial posterior vitreous de-

TABLE 3
FOLLOW-UP VITREOUS EXAMINATION IN EYES WITH NEOVASCULARIZATION
(N = 13)

	CONDITION AT INITIAL EXAMINATION		CONDITION AT DEVELOPMENT OF NEOVASCULARIZATION		CONDITION AT FINAL EXAMINATION	
VITREOUS DETACHMENT	NO.	(%)	NO.	(%)	NO.	(%)
No posterior vitreous detachment	11	(85)	9	(69)	6	(46)
Partial posterior vitreous detachment	1	(8)	1	(8)	6	(46)
Complete posterior vitreous detachment*	1	(8)	1	(8)	1	(8)
Unknown	0	(0)	2	(15)	0	(0)

*This patient may have had vitreous adhesion to the neovascularization.

tachment. No eyes developed complete posterior vitreous detachment during the follow-up period. Therefore, at the final vitreous examination, there was no posterior vitreous detachment in six eyes, and partial detachment in six eyes.

Discussion

We found that vitreous examination combined with evaluation of nonperfusion on fluorescein angiography was useful in predicting the development of neovascularization. The Kaplan-Meier plot showed 63% of Group 3 eyes (nonperfused retina and vitreous attached to the retina) would develop neovascularization three years from the first vitreous examination. Other groups had a low probability of its development (Groups 2 and 4, 0%; Group 1, 5%). The life table analysis in our study is not an accurate representation of the cumulative incidence of neovascularization from the onset of branch retinal vein occlusion, but rather it is the cumulative incidence of neovascularization from the first vitreous examination (average, 7.2 months after the onset of branch retinal vein occlusion; range, zero to 24 months).

The Branch Vein Occlusion Study[3] confirmed that nonperfusion was a significant risk factor for the development of neovascularization. Our results further suggest that knowing the vitreous condition increases the accuracy of predicting the development of neovascularization. Patients with no or partial posterior vitreous detachment and a large nonperfused retina are at high risk for the development of neovascularization and should be followed up closely.

Other groups of patients have less risk of developing neovascularization. Eyes with complete posterior vitreous detachment need not be examined as frequently for development of neovascularization, even if there are large areas of nonperfusion. It has been reported that neovascularization rarely develops in eyes with complete posterior vitreous detachment[4] or complete vitrectomy.[5] It also was shown that proliferative diabetic retinopathy rarely progressed in eyes with complete posterior vitreous detachment.[6] Although the mechanism is still unknown, it has been proposed that the posterior vitreous surface provided the necessary support for proliferation of preretinal fibrovascular tissue. Faulborn and Bowald,[7] using a special embedding method, showed that the fibrous material of the vitreous cortex was meshed with the newly formed proliferated tissue in proliferative diabetic retinopathy. Another explanation is that angiogenic substances produced by hypoxic retinal tissue diffuse more rapidly, so that the effect on adjacent retina is limited.[8] Vitreous fluorophotometry[9,10] and slit-lamp fluorography[11] have shown that the posterior vitreous membrane or the formed vitreous cortex acts as a barrier.

We used the El Bayadi-Kajiura lens to examine the vitreous, a technique that provides a wide illumination-observation angle with maximum vitreous mobility, a large image size, and far less distortion and glare than other methods currently available.[12,13] Many optical sections of the vitreous in each eye were carefully examined to avoid erroneous diagnoses. One eye was excluded from the analysis because cataract prevented adequate visualization of the vitreous. No neovascularization developed in this eye. We do not believe this exclusion led to bias. The vitreous condition of all selected eyes was confirmed at the first vitreous examination, and these data were used to analyze the prognostic value of vitreous examination. In this group of patients, there were few difficulties determining whether posterior vitreous detachment was present.

A disadvantage of vitreous examination using the El Bayadi-Kajiura lens is the inability to observe the vitreous anterior to the equator. Despite this disadvantage, observing the vitreous in the posterior pole and midperiphery is valuable for predicting the development of neovascularization in branch retinal vein occlusion. In our study, only one eye in which complete posterior vitreous detachment was diagnosed at the first vitreous examination developed neovascularization from the peripheral retina near the vitreous base. The vitreous condition of this eye might have been partial posterior vitreous detachment at the first vitreous examination, and the vitreous might have been attached to the neovascularization.

In 12 of the 13 eyes (92%) that developed neovascularization, there was no or partial posterior vitreous detachment. At least nine eyes (69%) developed neovascularization before any type of posterior vitreous detachment occurred. The presence of vitreoretinal attachment, with or without partial posterior vitreous detachment, seems to be important for neovascularization to begin. Neovascularization usually occurs in eyes with no posterior vitreous detachment. Early neovascularization was

shown to occur without vitreous detachment in diabetic retinopathy.[14] Some eyes probably developed partial posterior vitreous detachment after development of neovascularization because of shrinkage of the vitreous gel caused by leakage from new vessels or affected retina. The high percentage of partial posterior vitreous detachment in eyes with branch retinal vein occlusion[4] may result from development of partial posterior vitreous detachment after neovascularization.

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OPHTHALMIC MINIATURE

"How am I hearing this person through my arms?" "Am I seeing him with my face?" It is becoming clear to me that I see and hear with my entire body. The tensions in my stomach and back, the position of my head, the movements of my limbs, all affect the quality of my perception. If my legs are crossed and I open them, if I am leaning intently forward and I lean gently back, if my face is tight and I let the muscles go, then a small but measurable change takes place in all the sights and sounds around me.

Hugh Prather, *I Touch the Earth, the Earth Touches Me*
Garden City, Doubleday & Company, Inc., 1972, p. 119

Vitreous Surgery for Hemorrhagic and Fibrous Complications of Age-Related Macular Degeneration

Eugene de Juan, Jr., M.D., and Robert Machemer, M.D.

We applied vitreous surgical techniques in the treatment of hemorrhagic and fibrous complications of choroidal neovascular membranes by removing subretinal scars or hemorrhage, or both, in four patients. The surgical goals were achieved in all patients. Visual acuity improved in three patients. The major complication was recurrent detachment associated with large retinotomies.

AGE-RELATED MACULAR DEGENERATION is the major cause of blindness in persons over 55 years of age.[1] Recently, argon laser photocoagulation has been shown to be effective in preventing visual loss in a subgroup of patients with extrafoveal choroidal neovascular membranes.[2] However, these results have been tempered by a high recurrence rate[3] and a large proportion of eyes that do not meet criteria for treatment.[4] There are many patients who have suffered severe visual loss from the complications of macular degeneration. These complications include large serous retinal detachment (senile Coats' syndrome), subretinal hemorrhage, disciform scar formation, and breakthrough vitreous hemorrhage.[5-7]

Vitreous hemorrhage is an infrequent but well-known complication of age-related macular degeneration.[8] Vitreous surgery has been used to remove the hemorrhage from the vitreous cavity and thus improve vision.[8] We used vitreous surgical techniques to treat other complications of age-related macular degeneration, such as subretinal hemorrhages, serous retinal detachment, and subretinal scarring.

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Case Reports

Case 1

Visual acuity in this 71-year-old woman with a three-year history of decreased vision in both eyes was R.E.: 1/200 and L.E.: 20/70. Ophthalmoscopic examination showed a hemorrhagic serous retinal detachment of the macular area in the right eye (Fig. 1, left). This detachment had remained unchanged for 12 months. The left eye had areas of ectopic disciform degeneration nasally and drusen posteriorly. Vitrectomy was performed in the right eye to create an opening in the posterior vitreous surface. Diathermy was used to make two small posterior retinotomies at the edge of the detachment just superior to the temporal arcade. Subretinal fluid was drained by aspiration. The subretinal space was then washed by injecting and aspirating irrigating fluid. Fluid-gas exchange was performed and laser photocoagulation was placed around the retinotomies and in a scatter pattern over the area of previous detachment. Sulfur hexafluoride gas (20%) was injected into the vitreous cavity. After two years of follow-up, the retina has remained attached and visual acuity improved to 5/200 in the right eye (Fig. 1, right). During this same period visual acuity in the left eye decreased to 20/300 because of a subfoveal choroidal neovascular membrane causing disciform scarring.

Case 2

A 79-year-old man with a visual acuity of no light perception in his left eye had a two-week history of visual decrease to light perception in his right eye. Visual acuity was known to have been reduced before this episode to 20/400 because of age-related macular degeneration with subretinal scarring. Examination dis-

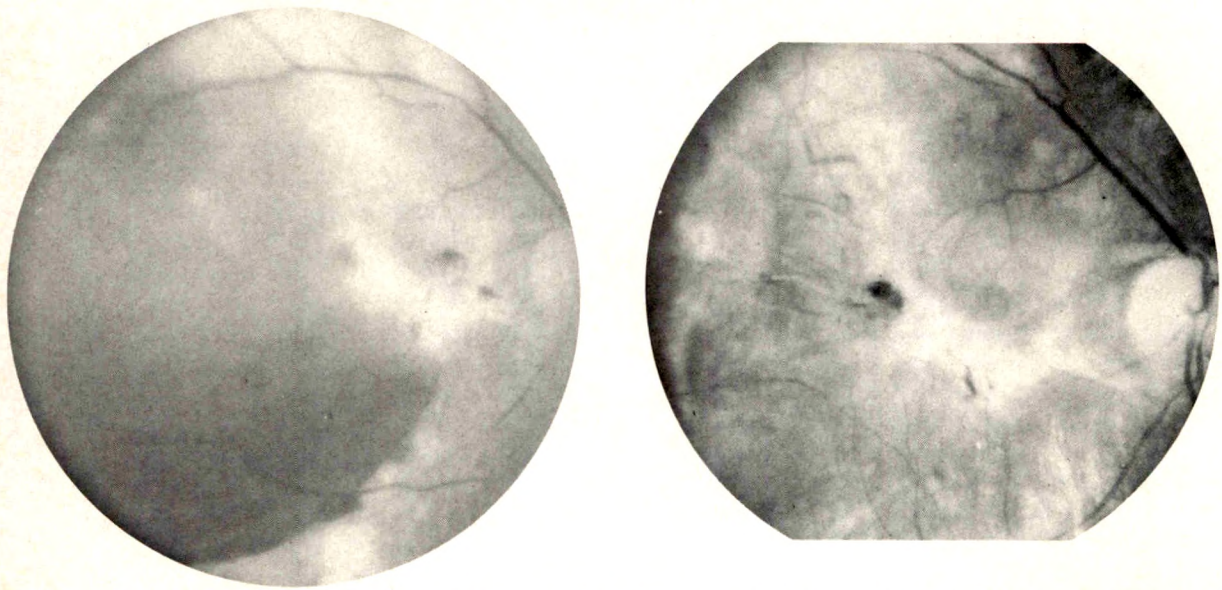


Fig. 1 (de Juan and Machemer). Case 1, right eye. Left, Preoperative fundus photograph of large submacular hemorrhage from age-related macular degeneration. Visual acuity was 1/200 (45-degree field). Right, Postoperative appearance after two years. Visual acuity was 5/200 (30-degree field).

closed a moderate vitreous hemorrhage, with a hazy view to the posteriorly elevated retina. Ultrasound examination showed a total retinal detachment with subretinal scarring and hemorrhage. The patient underwent vitrectomy. The vitreous was found to be attached to the posterior retina and was mechanically separated. The retina was totally detached by hemorrhagic subretinal fluid. Beneath the retina was a large submacular scar that extended to the arcades both superiorly and inferiorly. A retinotomy was performed superiorly and nasally and semisolid hemorrhagic subretinal fluid and scar tissue were removed by repeated fluid-gas exchanges expressing the fluid from the subretinal space. Some inferiorly located subretinal blood could not be removed. Endocryoretinopexy was placed around the retinotomy site and 20% sulfur hexafluoride gas was infused to fill the vitreous cavity. Postoperatively visual acuity rapidly increased to hand motions. The retina remained attached, with slow clearing of the remaining subretinal blood. The patient died suddenly of a myocardial infarction ten weeks after surgery. At that time he had been able to direct his ambulation visually.

Case 3

A 79-year-old man with known age-related macular degeneration (visual acuity of 20/200 in both eyes) had pain and a shadow-like sensation in his right eye for two months. On examination, visual acuity was R.E.: light perception and L.E.: 20/250. There was a moderate vitreous hemorrhage and a bullous retinal detachment in his right eye. Ultrasound demonstrated highly reflective subretinal fluid suggestive of subretinal blood beneath a total retinal detachment (Fig. 2, top left). A vitrectomy was performed to remove the vitreous hemorrhage and thin delicate membranes from the retinal surface. A 180-degree inferior retinotomy was performed peripherally, which allowed direct access to the subretinal blood and scar. The blood and scar were removed with a picforceps. There was only a single focal attachment of the scar to the choroid. Endolaser photocoagulation was placed along the edge of the retinotomy after fluid-gas exchange. Postoperatively the patient improved visually but developed an inferior retinal detachment with proliferative vitreoretinopathy. This was treated with epiretinal membrane removal and silicone oil tamponade. His visual acuity improved to 5/200 and the retina has remained attached for six months (Fig. 2, top right).

Histologic examination of the scar disclosed a fibrovascular membrane, with many of the known features of choroidal neovascular membranes (retinal pigment epithelial proliferation

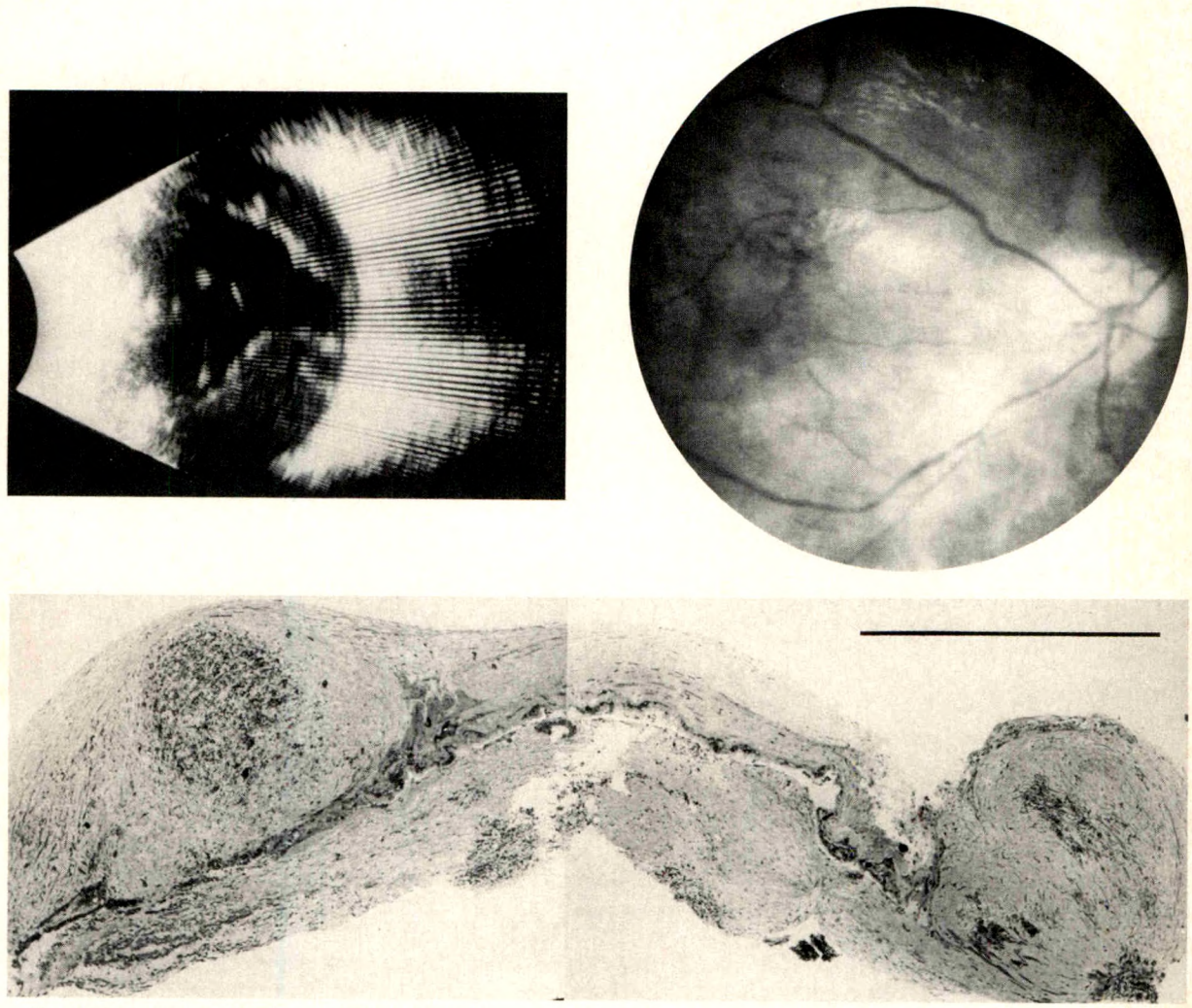


Fig. 2 (de Juan and Machemer). Case 3, right eye. Top left, Preoperative ultrasound showing total hemorrhagic retinal detachment. Visual acuity was light perception. Top right, Postoperative appearance of fundus showing no evidence of recurrent subretinal scarring or hemorrhage. Bottom, Histologic section of 4.5-mm subretinal scar (hematoxylin and eosin, bar = 1 mm).

and choroidal neovascular and fibrous proliferation) (Fig. 2, bottom).[9]

Case 4

This 71-year-old man had a two-month history of decreased vision in his right eye and a one-week history of blurred vision in his left eye. Visual acuity was R.E.: 2/200 and L.E.: 20/200. Ophthalmoscopic examination showed a subfoveal neovascular membrane with hemorrhage, serous fluid in the right eye, and fibrous scarring in both eyes. Because of rapidly increasing hemorrhage and scarring subretinally over a four-month observation period, we decided to treat the right eye surgically (Fig. 3, left). After removing clear vitreous and the posteriorly attached vitreous, a retinotomy was performed peripheral to the superior temporal arcade. The retina was peeled back and the exposed scar tissue was dissected bluntly from the retinal undersurface. The membrane appeared to have only a single focal attachment to the underlying choroid and was easily removed with a pic-forceps. The minimal bleeding that occurred stopped spontaneously. In an effort to place the foveal retina in an area of relatively normal pigment epithelium, a tack was used to stretch and pull the retina superiorly. After fluid-gas exchange, endocryoretinopexy was applied to the retinotomy edge. Postopera-

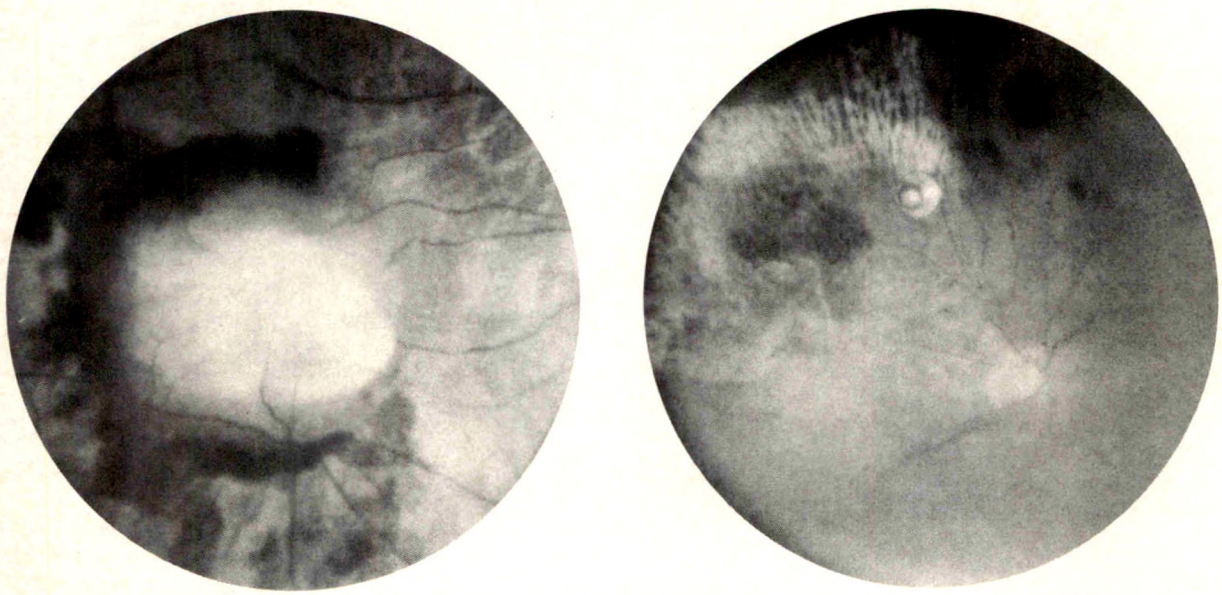


Fig. 3 (de Juan and Machemer). Case 4, right eye. Left, Preoperative fundus appearance of subfoveal disciform scar. Right, Postoperative appearance showing macular attachment with choroidal atrophy and tack pulling retina.

tively, visual acuity did not change (R.E.: 2/200) despite the removal of the scar (Fig. 3, right). Two months later, a localized peripheral retinal detachment occurred because fibrous proliferation caused the inferior edge of the retinotomy to elevate. This was not repaired. The posterior retina has remained attached for two years.

Discussion

Despite recent advances in the treatment of age-related macular degeneration, there are complications for which conventional treatments have no proven benefit, including extensive serous retinal detachment, extensive subretinal hemorrhage, and the subretinal scar itself.[3-7] Treatments that would improve visual acuity in affected individuals are not currently available.

We attempted to remove the subretinal blood and scarring associated with this disease in four patients by using vitreous surgical techniques. We found that it is possible to apply advanced vitreous surgical techniques to improve complications of age-related macular degeneration in some patients. Three of the four patients treated have had an objective visual improvement.

Subretinal hemorrhage was a significant component in all of our cases. In Patient 1, it did not clear for over one year. In Patients 2 and 3, subretinal hemorrhage was associated with total retinal detachment. In all patients, subretinal hemorrhage could be removed; however, the character varied from a semisolid material in the patients with extensive detachment (Patients 2 and 3) to a thinner blood-stained fluid in Patient 1. A fresher-appearing blood clot was present in Patient 4. The approach to removal of the blood varied from small retinotomies with irrigation of the subretinal space (Case 1), and multiple fluid-gas exchanges to express the blood (Case 2), to a large retinotomy (peripherally, Case 3; posteriorly, Case 4), to allow direct access to the subretinal space.

We removed subretinal scars in two patients. The scars were not broadly adherent to the underlying choroid as we had expected, but had only small connections. They could be removed without extensive hemorrhage or choroidal tearing. This corresponds to histologic evidence that shows usually a single vascular trunk passing through a disruption in Bruch's membrane.[9] Once the scar was removed, the area of retinal pigment epithelium and Bruch's membrane beneath the scar appeared normal except for some irregular pigmentation. This area was not directly involved in the fibrous

scarring process. Some pigment epithelium was probably removed from areas immediately adjacent to the entrance of the choroidal vessels through Bruch's membrane. During the postoperative course, which lasted over two years in two patients, we have observed little evidence of recurring scar formation. We did, however, change the status of the macula from a "wet" or scarred type to an atrophic or "dry" type.

Proliferative vitreoretinopathy appears to be a possible complication of this procedure. Patients 3 and 4 had recurrent detachment, and in both there was proliferation at the retinotomy edge. In Patient 3, the retina was successfully reattached after membrane peeling and silicone oil tamponade. Since vision did not improve in Patient 4, the persisting peripheral detachment was not treated. Clotted blood, retinal pigment epithelial cells, and macrophages associated with the subretinal scar may have stimulated the development of proliferative vitreoretinopathy when released into the vitreous cavity. Therefore, we try to minimize the exposure of the preretinal space to subretinal cells by carefully washing the vitreous cavity with infusion fluid.

Vision improved in all but Patient 4. In this patient, the subretinal membrane was adherent to the retinal undersurface and had to be dissected from it. This may have resulted in additional trauma to an already compromised and scarred outer retina. Based on this experience we do not believe that removal of an atrophic scar is likely to result in visual improvement. Zivojnovic[10] has suggested that submacular scars should only be removed when they are associated with rhegmatogenous retinal detachment.

The described surgery is a seemingly aggressive approach to a difficult problem. Many patients who have moderate visual impairment can use visual aids to remain functional. However, certain patients with unusually large and hemorrhagic serous detachments may benefit from such an approach. Questions regarding timing of intervention and ultimate patient benefit can be answered only after further experimental and clinical experience.

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OPHTHALMIC MINIATURE

He read, she thought, as if he were guiding something, or wheedling a large flock of sheep, or pushing his way up and up a single narrow path; and sometimes he went fast and straight, and broke his way through the bramble, and sometimes it seemed a branch struck at him, a bramble blinded him, but he was not going to let himself be beaten by that; on he went, tossing over page after page.

Virginia Woolf, *To The Lighthouse*
New York, Harcourt Brace Jovanovich, 1955, p. 283

Prostaglandin $F_{2\alpha}$-1-Isopropylester Lowers Intraocular Pressure Without Decreasing Aqueous Humor Flow

J. R. Kerstetter, M.S., R. F. Brubaker, M.D, S. E. Wilson, M.D., and L. J. Kullerstrand, B.S.

Using fluorophotometry, we performed a randomized, dose-response study of the effects of a prostaglandin derivative on aqueous humor flow. Prostaglandin $F_{2\alpha}$-1-isopropylester, 0.224 μg, 0.448 μg, and 1.120 μg, in saline with polysorbate 80 was instilled into one eye of 20 subjects in three separate dose studies. Polysorbate 80 in saline was instilled in the fellow eye as a control. The drug had no measurable effect on aqueous humor flow or corneal endothelial permeability. Intraocular pressure measured eight hours after administration of the highest dose, 1.120 μg, was 20% lower in the treated eye as compared to the fellow eye ($P < .001$).

PROSTAGLANDINS administered topically reduce intraocular pressure in several species.[1] For example, topical administration of prostaglandin $F_{2\alpha}$ (tromethamine salt) reduces intraocular pressure in rabbits.[2] Lee, Podos, and Severin[3] noted reductions in intraocular pressure in rabbits, cats, and monkeys after topically administered prostaglandin $F_{2\alpha}$ (tromethamine salt) in doses ranging from 250 to 1,000 μg. They observed no changes in aqueous humor flow as measured by fluorophotometry, but did observe significant increases in outflow facility as measured by tonography. Additional studies in cats and rhesus monkeys have shown that topically applied prostaglandin $F_{2\alpha}$ (tromethamine salt) produces a transient (15- to 30-minute) increase in intraocular pressure,[4] followed by a persistent decrease in intraocular pressure without development of tachyphylaxis when twice-daily doses are given.[5]

A study of owl monkey eyes showed that 1,000-μg doses of prostaglandin $F_{2\alpha}$ (tromethamine salt) can reduce intraocular pressure by 4.7 mm Hg in normal eyes and 25 mm Hg in glaucomatous eyes.[6] Crawford, Gabelt, and Kaufman[7] showed that 100-μg doses of topically administered prostaglandin $F_{2\alpha}$ (form not specified) produced an 8-mm Hg reduction in intraocular pressure and a reduction in aqueous humor flow in some but not all of their experiments using cynomolgus monkeys.[7] Camras and associates[8,9] noted a 10-mm Hg reduction of intraocular pressure in the same species without an accompanying reduction of aqueous humor flow after a 250-μg topical dose of prostaglandin $F_{2\alpha}$ (tromethamine salt). These investigators attributed the effect to changes of outflow facility.

In a study of 18 nonglaucomatous subjects, Giuffre[10] administered a 200-μg topical dose of prostaglandin $F_{2\alpha}$ (tromethamine salt) and noted significant reductions of intraocular pressure in treated eyes as compared to control eyes. The studies cited here have shown consistent reductions of intraocular pressure in several species with high doses of prostaglandin $F_{2\alpha}$.

Bito and Barody[11] have shown that the corneal epithelium acts as a barrier to prostaglandin $F_{2\alpha}$. Bito[12] has subsequently studied several esters of prostaglandin $F_{2\alpha}$ and found that methyl, ethyl, and isopropyl esters reduce intraocular pressure in cats at much lower doses than prostaglandin $F_{2\alpha}$. He also observed that the isopropyl ester of prostaglandin $F_{2\alpha}$ provided longer-term effects than the methyl or ethyl esters.

In a study of 0.1-, 0.5-, and 10-μg doses of prostaglandin $F_{2\alpha}$-1-isopropylester in six normal male volunteers, a dose-related reduction of intraocular pressure with a maximum reduc-

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tion eight hours after instillation was noted (A. Alm, M.D., and J. Villumsen, M.D., personal communication, 1985). The mean reduction of intraocular pressure eight hours after instillation was 5.7 mm Hg ($P < .02$). Villumsen and Alm[13] also studied 0.5-μg doses of prostaglandin $F_{2\alpha}$-1-isopropylester administered at 8 A.M. and 8 P.M. for one day to 12 glaucomatous patients. They observed intraocular pressure at eight, 12, and 24 hours after the first dose and noted mean reductions in pressure of 5.7 mm Hg ($P < .001$), 7.9 mm Hg ($P < .001$), and 7.3 mm Hg ($P < .005$), respectively.

The purpose of this study was to measure the rate of flow of aqueous humor in the human eye after the topical administration of a range of doses of prostaglandin $F_{2\alpha}$-1-isopropylester known to lower intraocular pressure.

Subjects and Methods

We selected 20 volunteers (11 men and nine women), ranging in age from 21 to 60 years, with no history of eye disease or significant systemic disease for the study. Subjects were excluded from the study for any of the following: (1) active ocular disease, (2) anatomic differences in the size and color of their eyes, (3) systemic drug use, (4) inability to undergo satisfactorily tonometry or fluorophotometry, (5) suspected hypersensitivity to drugs, or (6) participation in a trial of any other investigational drug within two weeks. The screening examination included a medical and ophthalmic history, visual acuity testing, slit-lamp examination, Goldmann applanation tonometry, and direct ophthalmoscopy. Written, informed consent according to federal guidelines was obtained from all subjects. Preliminary tests included photogrammetry to measure the volume of the anterior chamber.[14] Autofluorescence of each cornea was also measured.[15] Results of blood tests for pregnancy were negative two to three days before beginning the study in all female subjects.

Prostaglandin $F_{2\alpha}$-1-isopropylester was used as an ophthalmic solution at a concentration of 22.4 μg/100 ml. The drug was instilled by micropipette in 1-, 2-, and 5-μl doses, which contained 0.224, 0.448, and 1.12 μg of the investigational drug, respectively. The study was conducted under investigational new drug exemption No. 28,391 of the Food and Drug Administration.

Ten left and ten right eyes were randomly assigned to the study group. Each subject received a single 1-, 2-, and 5-μl dose of the test drug in the selected eye and a placebo (polysorbate 80 in saline) in the fellow eye in three separate studies spaced by a minimum of two weeks.

At 2 A.M. on the day of the study each subject instilled 2% fluorescein into each eye every three minutes for a total of five to ten instillations per eye. The number of instillations was individualized for each subject to produce the optimal concentration of fluorescein in the stroma.

Subjects reported to the testing area at 8 A.M. on the day of the study. Intensity and polarization of fluorescein were measured in both corneas and anterior chambers using the two-dimensional scanning fluorophotometer of McLaren and Brubaker.[16] After these measurements, the drug and placebo were instilled into the lower cul-de-sac of the subjects by micropipette; a total volume of 1, 2, or 5 μl was delivered containing 0.224 μg, 0.448 μg, and 1.120 μg of prostaglandin $F_{2\alpha}$-1-isopropylester, respectively. The subjects were instructed to keep their eyelids closed for four minutes after instillation to retard washout of the drug by tears. Hourly measurements of fluorescein in the cornea and anterior chamber were then made on all subjects.

Polarization of fluorescence was measured in each eye four to eight hours after instillation of the drug. At 4 P.M. on the day of the study (eight hours after drug instillation), intraocular pressure was measured in each eye by Goldmann applanation tonometry by one of us (S.E.W.) who did not know which eye had been treated. The measurements were taken three times, beginning with the right eye and alternating between eyes, and then averaged. Pretreatment intraocular pressures were measured in the same manner during the screening examination. Pretreatment intraocular pressures were not measured on the study day because of the confounding effect that fluorescein-containing topical anesthetics would have had on the measurement of aqueous humor flow by fluorophotometry. At the conclusion of the study, an ophthalmic examination was again performed. Each subject was queried about symptoms, and any symptoms reported were recorded.

Aqueous humor flow was calculated by a modification[17] of method 2 of Jones and Maurice.[18] The rate of clearance of fluorescein was

calculated as the rate of disappearance of fluorescein from the combined cornea and anterior chamber divided by the average fluorescent intensity in the anterior chamber during that interval. The rate of diffusional clearance of fluorescein was assumed to be 0.25 μl/minute.[19]

Results

All 20 subjects completed the study of the 1- and 2-μl doses. However, two subjects complained of pain and photophobia and were noted to have marked conjunctival hyperemia for several hours after instillation of the 2-μl dose. They were excluded from tests of the 5-μl dose.

Neither of the two smaller doses caused a significant reduction of intraocular pressure eight hours after instillation (Table 1). The highest dose produced an ocular hypotensive effect that was significant eight hours after instillation. Intraocular pressure was 11.8 ± 2.8 mm Hg in the treated eye and 14.4 ± 3.0 mm Hg in the untreated eye, a difference of approximately 20% ($P < .001$).

We were unable to demonstrate any effect of the drug on the rate of aqueous humor flow. The flow was in the range of 2.5 to 2.9 μl/minute under all conditions of the experiment. The rates of flow were generally higher in the morning than the afternoon in both the treated eye and the fellow eye (Table 2), a difference that can be attributed to the diurnal variation of aqueous humor flow in humans.

The permeability of the corneal endothelium to fluorescein was not significantly altered by prostaglandin $F_{2\alpha}$-1-isopropylester (Table 3), nor was there any evidence from polarization of fluorescence in the cornea or anterior cham-

TABLE 1
EFFECTS OF PROSTAGLANDIN $F_{2\alpha}$-1-ISOPROPYLESTER ON INTRAOCULAR PRESSURE

	INTRAOCULAR PRESSURE (MM HG)			
	PRETREATMENT		8 HOURS POSTTREATMENT	
DOSE	MEAN	S.D.	MEAN	S.D.
1 μl (0.224 μg)				
Drug	14.7	2.6	12.9	2.6
Placebo	14.1	2.3	14.0	2.9
	N = 19		N = 20	
2 μl (0.448 μg)				
Drug	14.4	2.4	13.6	3.6
Placebo	14.4	2.5	13.4	2.7
	N = 19		N = 20	
5 μl (1.12 μg)				
Drug	14.4	2.3	11.8*	2.8
Placebo	14.6	2.7	14.4*	3.0
	N = 17		N = 18	

*Difference between drug-treated and placebo-treated eyes was significant ($P < .001$) using two-tailed *t*-test.

TABLE 2
EFFECTS OF PROSTAGLANDIN $F_{2\alpha}$-1-ISOPROPYLESTER ON AQUEOUS HUMOR FLOW (μL/MIN)*

	MORNING (8 A.M.–NOON)		AFTERNOON (NOON–8 P.M.)		AVERAGE (8 A.M.–8 P.M.)	
DOSE	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.
1 μl (N = 20)						
Drug	2.72	0.72	2.65	0.47	2.69	0.60
Placebo	2.86	0.77	2.66	0.50	2.76	0.64
2 μl (N = 20)						
Drug	2.88	0.45	2.67	0.49	2.78	0.47
Placebo	2.78	0.62	2.65	0.47	2.72	0.55
5 μl (N = 18)						
Drug	2.67	0.48	2.68	0.53	2.68	0.51
Placebo	2.52	0.47	2.50	0.40	2.51	0.44

*Differences between drug-treated and placebo-treated eyes were not significant.

TABLE 3
EFFECTS OF PROSTAGLANDIN $F_{2\alpha}$-1-ISOPROPYLESTER ON ENDOTHELIAL PERMEABILITY (CM/MIN × 10^{-4})*

	MORNING (8 A.M.–NOON)		AFTERNOON (NOON–8 P.M.)		AVERAGE (8 A.M.–8 P.M.)	
DOSE	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.
1 μl (N = 20)						
Drug	3.56	0.96	4.00	0.72	3.78	0.84
Placebo	3.69	0.68	3.94	0.63	3.82	0.66
2 μl (N = 20)						
Drug	3.79	0.63	3.66	0.58	3.73	0.61
Placebo	3.70	0.70	3.65	0.46	3.68	0.58
5 μl (N = 18)						
Drug	3.57	0.58	3.99	0.48	3.78	0.53
Placebo	3.52	0.62	3.91	0.66	3.72	0.64

*Differences between drug-tested and placebo-treated eyes were not significant.

TABLE 4

EFFECTS OF PROSTAGLANDIN $F_{2\alpha}$-1-ISOPROPYLESTER ON POLARIZATION OF FLUORESCENCE*

	PRETREATMENT				POSTTREATMENT			
	CORNEA		ANTERIOR CHAMBER		CORNEA		ANTERIOR CHAMBER	
DOSE	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.
1 μl (N = 20)								
Drug	0.167	0.036	0.031	0.023	0.176	0.043	0.033	0.018
Placebo	0.165	0.030	0.025	0.016	0.174	0.025	0.027	0.012
2 μl (N = 20)								
Drug	0.154	0.022	0.023	0.016	0.175	0.023	0.019	0.011
Placebo	0.157	0.023	0.027	0.020	0.184	0.038	0.023	0.013
5 μl (N = 18)								
Drug	0.171	0.023	0.026	0.014	0.188	0.022	0.026	0.015
Placebo	0.172	0.026	0.028	0.017	0.189	0.021	0.026	0.012

*Differences between drug-treated and placebo-treated eyes were not significant.

ber that the drug had caused a breakdown of the blood-aqueous barrier (Table 4). In this experiment, polarization of fluorescence is used to measure any changes in the polarization characteristics of the cornea or anterior chamber that would occur in response to the presence of additional proteins from breakdown in the blood-aqueous barrier.

Two subjects had moderate redness for several hours and ocular discomfort after the 2-μl dose. Otherwise, the drug was well tolerated. All subjects had conjunctival hyperemia that lasted one to several hours after instillation.

Discussion

This study confirms the observations of others[11] that low doses of topically applied prostaglandin esters can reduce intraocular pressure. This pressure lowering effect must be the result of effects on outflow since we did not observe any decrease in the rate of clearance of fluorescein. Since no significant changes in the rate of aqueous humor flow were noted, we calculated the statistical power of the experiment based on a previous study of 71 normal, untreated subjects, in whom the variance of our measurement technique was determined. In the present experiment where n = 20, the probability of detecting an 18% change in flow is 95%. There is a 50% chance that we would have detected changes in flow of approximately 10%. We believe, as did Camras and associates[8,9] and Lee, Podos, and Severin,[3] that prostaglandin $F_{2\alpha}$ has no clinically significant effect on aqueous humor flow and that its ocular pressure lowering effect must be mediated via the outflow system.

Compared to the four major classes of therapeutic ocular hypotensive agents currently used for the treatment of glaucoma—cholinergics, adrenergic agonists, adrenergic blockers, and carbonic anhydrase inhibitors—prostaglandin $F_{2\alpha}$ appears to have effects that are most similar to adrenergic agonists, such as epinephrine. First, epinephrine's effect may be the result of endogenous prostaglandin release.[20,21] Second, both epinephrine[22] and prostaglandin $F_{2\alpha}$[7] are thought to enhance uveoscleral outflow. However, ocular hypotensive response to prostaglandins may also be the result of unique mechanisms not shared by any currently used therapeutic agents.

Acknowledgment

Pharmacia AB, Uppsala, Sweden, supplied the prostaglandin $F_{2\alpha}$-1-isopropylester.

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OPHTHALMIC MINIATURE

One case of acute and two cases of chronic glaucoma were treated by excisions of a portion of the iris in each eye. The acute case completely recovered with capillary hemorrhage; the two chronic cases are improving.

In cases in which the operation has been successfully performed, the aqueous humour is not accumulated in the anterior chamber, but appears to escape through the wound as it is secreted. No active inflammatory symptoms have occurred after treatment as one would expect after so severe an operation.

British Medical Journal, March 6, 1858, p. 181

Response of Blood Flow to Warm and Cold in Normal and Low-Tension Glaucoma Patients

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We measured blood flow in the finger in 38 control subjects with normal ocular findings without migraine, 13 control subjects with normal ocular findings with classic migraine, 17 patients with low-tension glaucoma with classic migraine, and 29 patients with low-tension glaucoma without migraine. Three blood flow measurements were recorded: one at baseline, one after immersion in warm water (40 C), and one after ten seconds' exposure to cold water (4 C). The mean baseline flow and the mean flow after exposure to cold was lower in patients with low-tension glaucoma ($P = .013$ and $P < .001$, respectively).

THE MECHANISM of damage to the optic nerve in low-tension and chronic open-angle glaucoma is unknown. Whether the damage is mechanical as a result of intraocular pressure, ischemia, or both is unclear. The occurrence of low-tension glaucoma suggests that factors other than intraocular pressure may be responsible for some of the pathogenic events. In 1985 Phelps and Corbett[1] found that 47% of their patients with low-tension glaucoma suffered from migraine. This suggested for the first time that vasospastic events might play a role in the progressive changes of the optic nerve head in low-tension glaucoma. Migraine is associated with other vasospastic diseases, such as variant angina and Raynaud's disease. Blood flow to tissues is known to depend on the pressure head (in the eye this is the difference between the vascular blood pressure and the intraocular pressure), blood viscosity, and the local resistance of the circulation determined principally by the diameter of the blood vessels. During increased metabolic demand, vasodilatation reduces the resistance to flow. However, if vasodilatation does not occur or if blood vessels are in spasm, the tissue may become ischemic. Such an ischemia may be temporary.

In 1986 Gasser and associates[2] described an ocular vasospastic syndrome in which patients with unexplained scotomas producing visual loss had abnormal capillaroscopic responses to cold in the nail fold of the finger. The findings in some of these patients resembled findings in patients with low-tension glaucoma. Many of these patients also suffered from cold hands and their visual field defects became aggravated by the immersion of a hand in cold water. The scotomas often improved after the administration of calcium channel blockers. In a more recent study, Guthauser, Flammer, and Mahler[3] found statistically significant associations between the capillaroscopic cold response and a history of cold hands and feet. The history of cold hands and feet was also related to the visual field change produced by the immersion of the hand in cold water. Additionally, the visual field deterioration was associated with the abnormal digital responses to cold on capillaroscopy. In 1959 Fisher,[4] in his study on extracranial cerebral vascular disease, found that migraine may have been the cause of transient monocular visual field loss in 24 of 138 eyes.

We studied the occurrence of vasospasm in the finger in a group of control subjects with normal eyes with and without classic migraine, and a group of patients with low-tension glaucoma with and without classic migraine.

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Patients and Methods

We examined 38 subjects who had normal ocular findings in both eyes without classic migraine and 13 subjects who had normal ocular findings with classic migraine as well as 29 patients with low-tension glaucoma without migraine and 17 patients with low-tension glaucoma with classic migraine. Low-tension glaucoma was defined as a characteristic optic nerve head change with classic visual field defects of the nerve fiber bundle type. Intraocular pressure, including diurnal measurements, was no greater than 22 mm Hg. In all patients a probe of the laser Doppler flow meter was attached to the skin of the middle finger. A baseline flow in arbitrary flow units was recorded until a steady baseline reading was achieved (Fig. 1). The hand was then immersed in warm water (40 C) for two minutes, wrapped in a towel, and the flow was monitored until a maximum flow was reached. The hand was then placed in ice cold (4 C) water for ten seconds, and the flow was monitored for the next several minutes. Blood pressure was also recorded.

We found that most normal subjects without migraine had a warm hand and a correspondingly good baseline flow. They had little increase in flow after exposure to the warm water. They showed a decrease in flow during and after a short exposure to cold, but the flow quickly returned to baseline (Fig. 1). In normal subjects with classic migraine, the baseline flow was low. In some of these subjects, exposure to warm water produced a large increase in flow and exposure to cold water caused a decrease in flow that persisted (Fig. 2). We called this the vasospastic response. Other normal subjects with migraine had a good baseline flow with little vasodilatation in warm water, but a marked, persistent diminution in flow after exposure to cold (Fig. 3).

Measurements of the baseline flow, the maximum flow after immersion in warm water, and the flow after exposure to cold water as well as ratios of maximum flow over baseline flow and maximum flow over after-cold flows were available for analysis. Analyses of the flows were performed on the raw data; however, the ratios were logarithmically transformed to reduce skewness and to stabilize the variances. Univariate analyses of variance and of covariance, and discriminant analyses were performed. The latter were performed to separate patients with normal ocular results with and without classic migraine from patients with low-tension glaucoma with and without migraine using both the transformed ratios of maximum flow over baseline flow and of maximum flow over after-cold flow. Discriminant analyses were also performed on the groups with respect to measurements of raw baseline flow, and

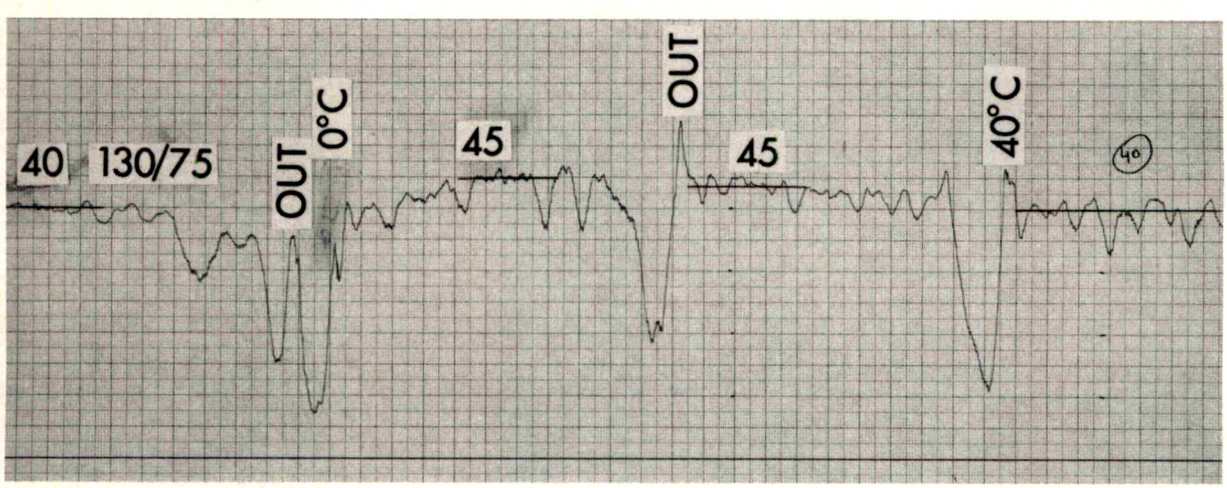


Fig. 1 (Drance and associates). Tracing of total flow in an individual with normal ocular findings without classic migraine. The tracing shows a good normal baseline flow of 40 units and no increase in flow after immersion of the hand in warm water. There is a diminution of the flow after a ten-second exposure to cold, with a rapid recovery to baseline (blood pressure, 130/75 mm Hg).

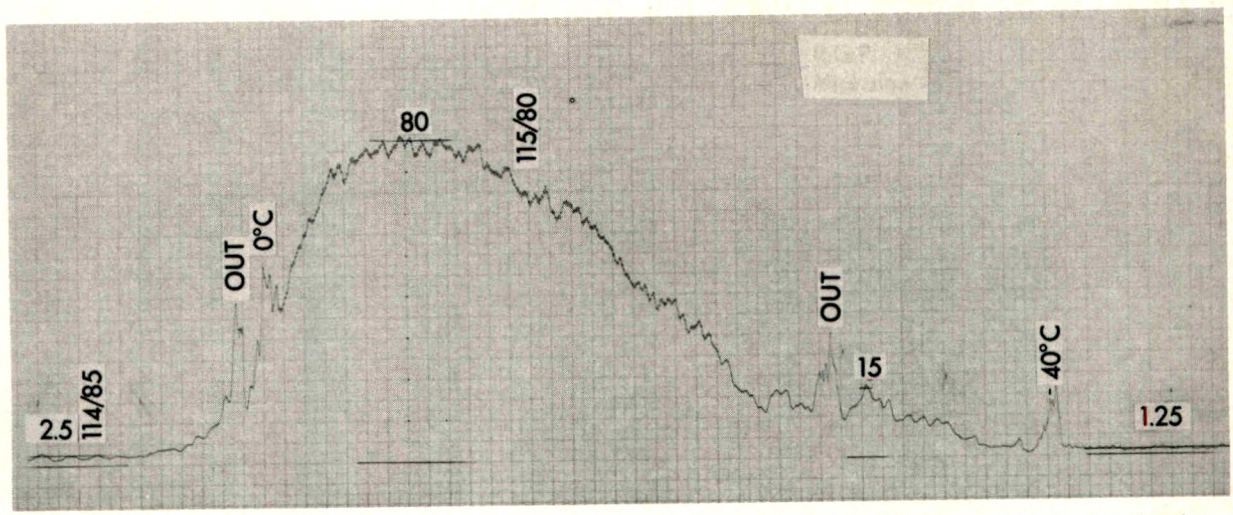


Fig. 2 (Drance and associates). Tracing of flow in a patient with normal ocular findings with classic migraine. The baseline flow is low, with a great increase after immersion in warm water (blood pressure, 115/80 mm Hg). A marked diminution of flow occurred after exposure to cold, with no recovery (blood pressure, 114/85 mm Hg).

flow after exposure to both warm and cold. The distributions of the raw ratios were also compared using nonparametric methods (Wilcoxon's rank sum test). Thirty one of the normal and low-tension glaucoma patients were tested twice in order to assess the reproducibility of the measurements. The low baseline flow and the low after-cold flow readings were correctly reproduced 83% and 84% of the time, respectively.

Results

The mean age of the normal subjects was 55.4 ± 14.4 years, whereas patients in the low-tension glaucoma group had a mean age of 63.88 ± 12.5 years. This difference was statistically significant ($P < .001$). However, in the normal subjects, the baseline flow and the flows after warm and cold as well as their ratios were not

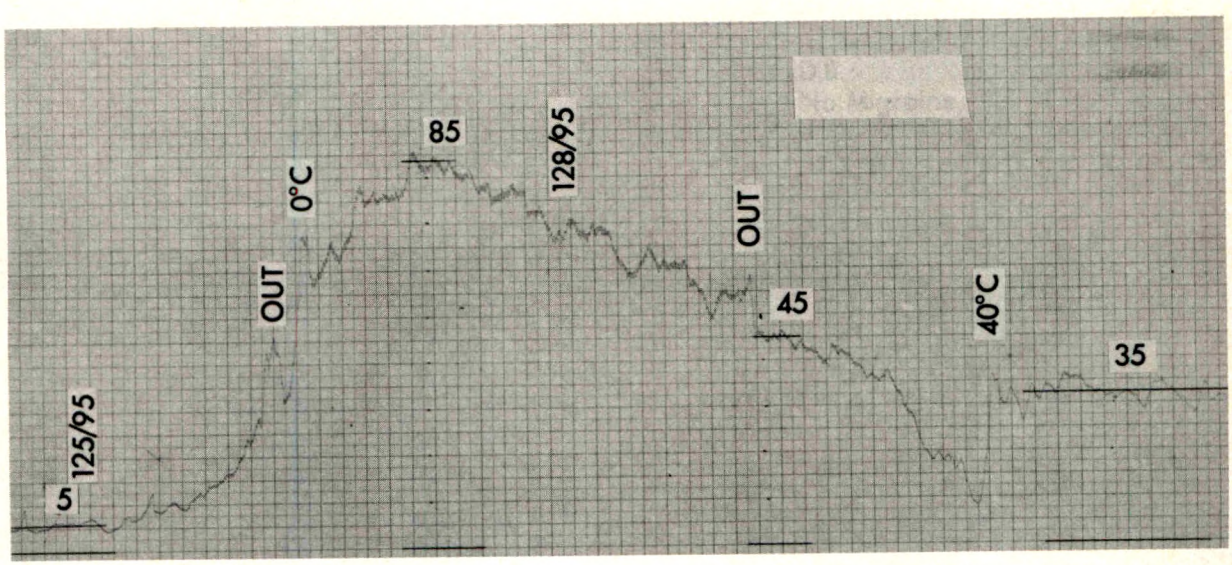


Fig. 3 (Drance and associates). Tracing of flow in a patient with normal ocular findings without migraine showing good baseline flow followed by some increase in flow after immersion in warm water (blood pressure, 128/95 mm Hg). There is a marked response to cold, with no recovery (blood pressure, 125/95 mm Hg).

TABLE 1
COMPARISON OF FLOW BETWEEN CONTROL SUBJECTS WITH AND WITHOUT MIGRAINE (ARBITRARY UNITS)

FLOW (MEAN ± S.D.)	NO MIGRAINE (N = 38)	MIGRAINE (N = 13)	P VALUE*
Baseline flow	36.07 ± 20.71	32.48 ± 26.61	NS
Flow after heat	66.56 ± 16.15	80.00 ± 12.56	.007
Flow after cold	24.32 ± 20.89	18.36 ± 16.55	NS

*NS, not significant.

related to age or to systemic blood pressure. Therefore, the observed differences in age were unlikely to affect the analyses.

In the subjects with normal ocular findings, the mean baseline flow in subjects without migraine was not statistically different from those with classic migraine (Table 1). After immersion in warm water, however, subjects with migraine showed a significantly greater flow than those without migraine ($P = .007$). After exposure to cold, the subjects with migraine showed a lower mean flow than those without, but the difference was not statistically significant.

The distributions of the maximal flow/after-cold flow ratios of seven or greater in the subjects with normal ocular findings without migraine were compared nonparametrically to those with classic migraine using the Wilcoxon two-sample rank sum test. Ten of 38 control subjects (26%) without migraine and eight of 13 (64%) with classic migraine had a ratio of seven or more ($P = .068$).

The mean baseline flow in patients with low-tension glaucoma without migraine was significantly lower than in subjects with normal eyes without migraine ($P < .01$) (Table 2). There was no statistically significant difference between these two groups in their mean response to warmth, but after exposure to cold the patients with low-tension glaucoma showed a significantly lower flow than the normal subjects ($P < .001$). The ratio of the maximum flow over flow after cold was also higher in the patients with low-tension glaucoma than in the normal subjects ($P = .007$). The mean of the ratio of the maximum flow over baseline flow was almost twice as high in the patients with low-tension glaucoma than in the normal subjects, but the difference was not statistically significant.

The distributions of the maximum flow/after-cold flow ratios in the normal subjects without migraine and those with low-tension glaucoma without migraine were compared nonparametrically using the Wilcoxon two-sample rank sum test. In 19 of 29 of patients (65%) with low-tension glaucoma and ten of 38 of normal subjects (26%) without migraine, this ratio was greater than or equal to seven ($P < .0001$).

There was no significant difference in the distributions of the ratio between the patients with low-tension glaucoma without migraine and the normal subjects with migraine.

TABLE 2
COMPARISON OF FLOW BETWEEN CONTROL SUBJECTS WITHOUT MIGRAINE AND LOW-TENSION GLAUCOMA PATIENTS WITHOUT MIGRAINE (ARBITRARY UNITS)

FLOW (MEAN ± S.D.)	CONTROL SUBJECTS WITHOUT MIGRAINE (N = 38)	LOW-TENSION GLAUCOMA PATIENTS WITHOUT MIGRAINE (N = 29)	P VALUE*
Baseline flow	36.07 ± 20.71	22.70 ± 21.82	.013
Flow after heat	66.56 ± 16.15	70.52 ± 21.40	NS
Flow after cold	24.32 ± 20.89	8.02 ± 5.98	<.001
Flow after heat ÷ flow after cold	6.39 ± 6.72	14.81 ± 16.88	.007
Flow after heat ÷ baseline flow	4.68 ± 7.43	8.09 ± 7.93	NS

*NS, not significant.

Discussion

The high prevalence of migraine among patients with low-tension glaucoma reported by Phelps and Corbett[1] suggested that vasospastic disease might account for the pathologic events at the optic nerve. We found that in nonglaucomatous subjects, 26% without migraine had a vasospastic response after exposure to cold, while 64% with classic migraine showed such a response. Of the patients with low-tension glaucoma without classic migraine, 65% showed a vasospastic response. This was similar to the frequency noted in nonglaucomatous subjects with migraine. Gasser and associates,[2] in their study of the capillary circulation in the finger by means of capillaroscopy, also found that patients with vasospastic diseases of the eye had an abnormal response to cold. Their

patients often reported cold hands and feet, even in the summer, and had an abnormal capillaroscopic response to cold when visual acuity was measured while a limb was immersed in cold water. Guthauser, Flammer, and Mahler[3] further described patients with low-tension glaucoma in whom an abnormal capillaroscopic response was present in the absence of migraine and who responded favorably to treatment with calcium channel blockers.

Studies of the influence of vasospasm in some patients with low-tension glaucoma are necessary as are studies of the possible use of antivasospastic medication in these patients to determine if the disease process can be modified.

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OPHTHALMIC MINIATURE

Both the blossoms and the fruit of the pomegranate tree (*Punica granatum*) were employed by various ancient Greco-Roman physicians in almost all diseases of the eye. Pliny, with characteristic inclination toward the wonderful, declares that if a person, who is wearing neither shoes, girdle, nor ring, plucks a pomegranate blossom with the thumb and fourth finger of the left hand, and then very gently, touches the flower to his wide-open eyes, then sticks it in his mouth, and without permitting the teeth to touch it, swallows it, he will be protected against all disease of the eye for a full year from that very moment.

Casey A. Wood, editor, *The American Encyclopedia and Dictionary of Ophthalmology*
Chicago, Cleveland Press, 1918

The Lenz Microphthalmia Syndrome

Elias I. Traboulsi, M.D., Widukind Lenz, M.D., Mario Gonzales-Ramos, M.D., Jacqueline Siegel, M.D., William G. Macrae, M.D., and Irene H. Maumenee, M.D.

We examined two patients with the Lenz microphthalmia syndrome. When findings from these two patients and those from ten other patients in the literature were combined, the following abnormalities were observed: microphthalmos in all patients; developmental retardation in 11 patients (92%); external ear abnormalities in ten patients (83%); microcephaly in ten patients (83%); blepharoptosis in nine patients (75%); skeletal anomalies (excluding digital anomalies) in eight patients (67%); dental abnormalities of number and position in eight patients (67%); digital anomalies in seven patients (58%); urogenital anomalies in six patients (50%); and cleft lip and palate abnormalities in four patients (33%). Cardiac anomalies, imperforate anus, hearing loss, spastic diplegia, sacral pits, webbed neck, and abnormal dermatoglyphs were rarely seen. One of our two patients had a dislocated lens and retinal detachment.

AN X-LINKED MALFORMATION syndrome characterized by microphthalmia, mental retardation, and aural, digital, skeletal, and urogenital anomalies was first described by Lenz in 1955.[1] Since then three additional pedigrees[2-4] and four isolated cases[5-8] have been reported. We examined two unrelated patients with this syndrome as well as the postmortem findings on Lenz's original patient. A review of published cases provides data on the manifestations of this syndrome.

Case Reports

Case 1

This boy was first seen at age 3 years. He was born at full term after an uncomplicated pregnancy and normal vaginal delivery. Birth weight was 2,430 g. He was a poor feeder and was hospitalized for the first six weeks of life because of feeding difficulties. He sat at 6 months, stood alone at 10 months, and walked at 20 months. His mental development was slightly subnormal at age 3 years. On physical examination at that time his head circumference, weight, and height were all below the fifth percentile. He had a long face, microphthalmic eyes, and abnormal ears that were low set, posteriorly rotated, and had poorly developed antihelices (Fig. 1). His teeth were

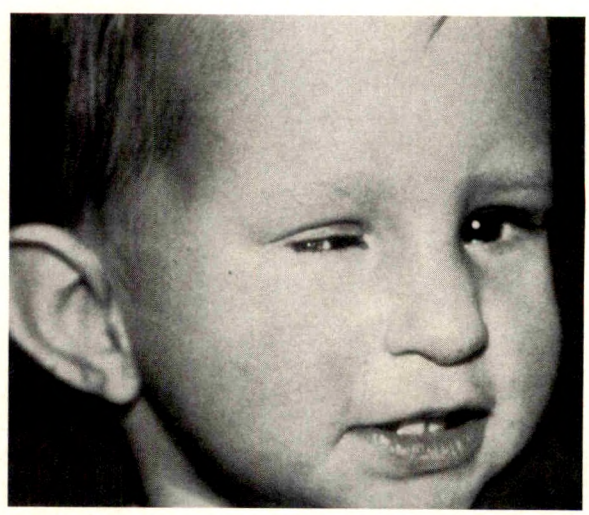


Fig. 1 (Traboulsi and associates). Patient 1. Note bilateral microphthalmos, more severe on the right, vertically shortened right palpebral fissure, and thin, anteverted ears.

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widely interspaced and his palate was normal. No heart murmurs were heard and his genitalia were normal. The right hand was smaller than the left and had a hypoplastic thumb. There was medial clinodactyly of the left fourth and fifth toes. Ocular examination disclosed right blepharoptosis and bilateral colobomatous microphthalmia, with corneal diameters of R.E.: 5.5 mm and L.E.: 10 mm. Nystagmus was present and exact visual acuity could not be obtained. Ophthalmoscopic examination showed bilateral colobomata extending to the optic disks. At age 3 years, cycloplegic refraction of the child's left eye showed −7.00 +1.00 × 90; refraction was not possible in the smaller, right eye. The patient's mother is of German descent and had a number of similarly affected male relatives, none of whom were available for examination. Results of her physical and ocular examinations were unremarkable.

Case 2

This 5-month-old boy was born at full term to nonconsanguineous parents after an uneventful pregnancy and a normal vaginal delivery. He had multiple congenital anomalies, including bilateral microphthalmia and iris colobomata, external ear abnormalities, imperforate anus, hypospadias, and finger and toe abnormalities (Figs. 2 and 3). The ears were cup-shaped, with a left preauricular tag. Audiologic examination done at age 14 months demonstrated a mild hearing loss (probably mixed conductive/neural), and the child was fitted with hearing aids, which improved his performance markedly. The right hand had four normal digits and preaxial duplication of the thumb. In the left hand the thumb was partially duplicated. The right foot showed an appendage to the second toe and syndactyly of the third and fourth toes. There was syndactyly of the second and third left toes. Ophthalmologic examination showed relatively good fixation with either eye, despite nystagmus and a variable esotropia. The height of the palpebral fissures measured 8 mm on the right and 4 mm on the left. Vertical corneal diameters measured 11 and 6 mm in the right and left eyes, respectively. There were typical colobomata of the iris and choroid in each eye. Cycloplegic retinoscopy showed −8.00 diopters over the coloboma and −3.50 diopters over the retina in the right eye and +7.50 diopters in the left eye. In the right fundus the coloboma involved the optic disk (Fig. 4). In the left eye there was a big excavation (posterior staphyloma) at the site of exit of the retinal blood vessels, with normal-appearing retina nasally and temporally above the coloboma.

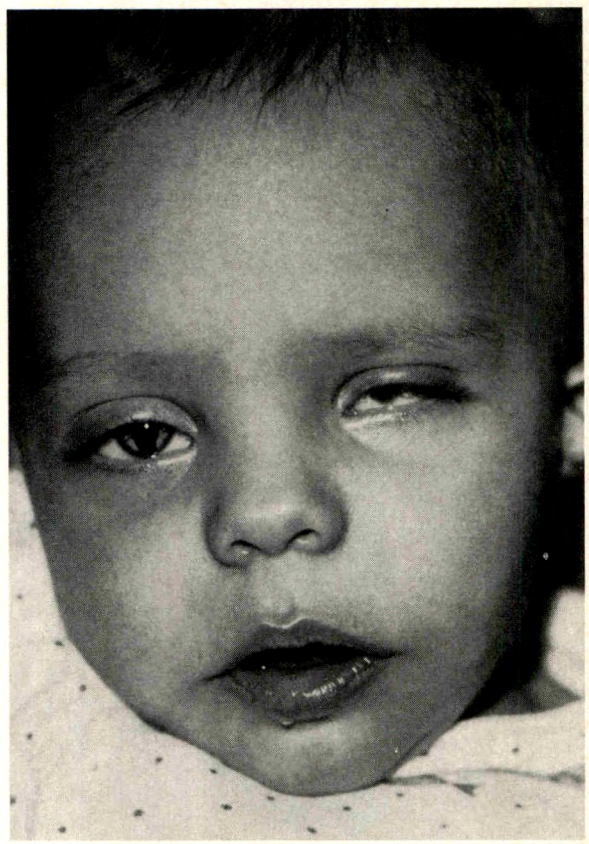


Fig. 2 (Traboulsi and associates). Patient 2. Bilateral colobomatous microphthalmia.

A karyotype was normal. Family history was noncontributory. Results of the mother's physical and ocular examinations were normal.

The child was examined under anesthesia at the age of 12 months because of suspicion of a retinal detachment in the left eye. Findings in the right eye were unchanged. The left lens was subluxated inferiorly and a total retinal detachment with proliferative vitreoretinopathy was present (Fig. 5). The detachment was judged to be inoperable and no reattachment surgery was performed.

Postmortem Findings on Lenz's Original Patient

This patient died of complications of uremia at age 28 years. Autopsy findings included bicuspid aortic valve with mild coarctation of the aorta; aplasia of the left kidney, ureter, and renal vessels; hydronephrosis of the right kidney with parenchymal atrophy; cryptorchid-

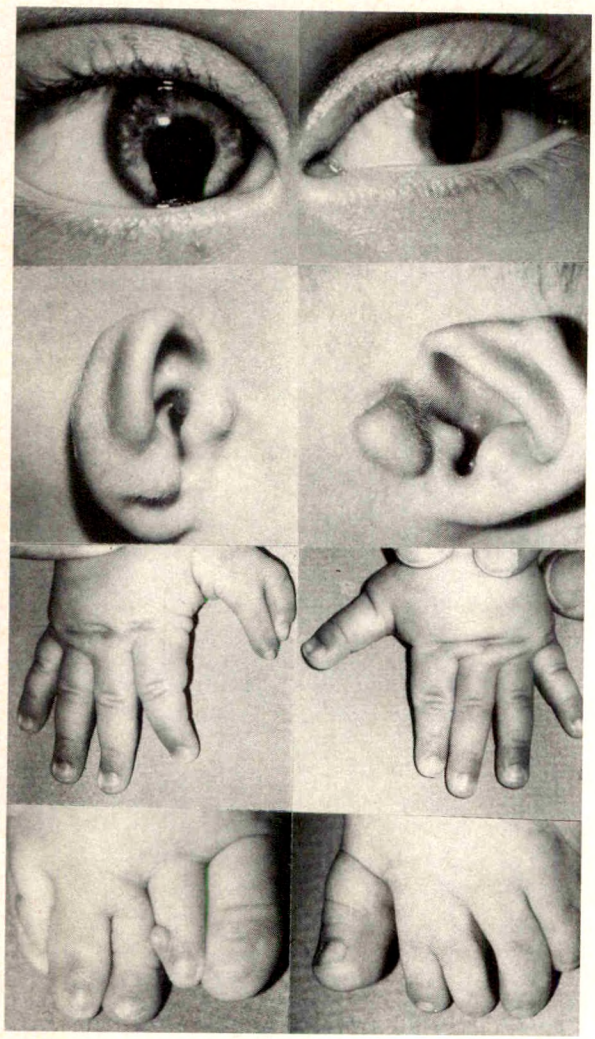


Fig. 3 (Traboulsi and associates). Patient 2. Composite figure showing right and left eyes, external ears, hands, and toes.

ism; and spina bifida occulta. The physical and ocular findings were described in Lenz's original publication.[1]

Literature Review

Table 1 summarizes the physical and ocular findings as well as pertinent family history and findings in the ten cases previously reported in the literature, and in the two cases reported here. We included only patients for whom adequate clinical information was available. The family studied by Ogunye, Murray, and Osgood[9] is the same as that described by Hoefnagel, Keenan, and Allen.[2] The family described by Dinno and associates[4] as having

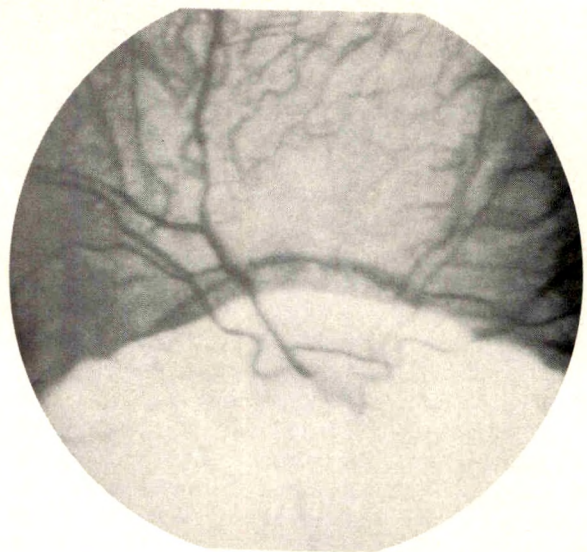


Fig. 4 (Traboulsi and associates). Right fundus, Patient 2. Note large chorioretinal coloboma involving the optic nerve head.

a new hereditary syndrome probably has the Lenz syndrome, as does the family described by Goldberg and McKusick.[3] The available clinical information on the family described by Cuendet[10] is not sufficient to permit its inclu-

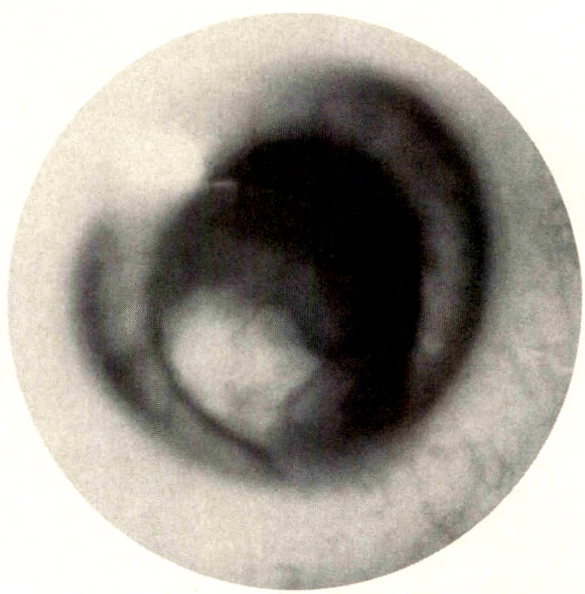


Fig. 5 (Traboulsi and associates). Left eye, Patient 2. Note iris coloboma, subluxated lens, and retinal detachment.

TABLE 1
ABNORMALITIES IN 12 PATIENTS WITH THE LENZ MICROPHTHALMIA SYNDROME*

STUDY	MICROPH-THALMOS	BLEPHARO-PTOSIS	MICRO-CEPHALY	RETAR-DATION	EAR ABNOR-MALITIES	CLEFT LIP/ PALATE	DENTAL ANOMALIES	SKELETAL ANOMALIES	DIGITAL ANOMALIES	UROGENITAL ANOMALIES	OTHER ANOMALIES	FAMILY HISTORY
Lenz[1]												
Proband	Yes	NA	NA	NA	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Hoefnagel, Keenan, and Allen[2]												
Proband	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No	Yes
Goldberg and McKusick[3]												
Proband	Yes	Yes	Yes	Yes	NA	No	No	Yes	No	No	No	Yes
III-4	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	No	Yes
III-8	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No	Yes
Dinno and associates[4]												
Proband	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	NA	No	Yes
Hermann and Opitz[5]												
Proband	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Baraitser, Winter, and Taylor[6]												
Proband	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Glanz and associates[7]												
Proband	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Pallota[8]												
Proband	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Present study												
Case 1	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes
Case 2	Yes	Yes	No	Yes	Yes	No	No	No	Yes	Yes	Yes	No

*NA, information not available.

sion in Table 1; additionally, patients in that family had cataracts, a finding that has not been observed in patients with more definite Lenz syndrome.

Discussion

The differential diagnosis of microphthalmia combined with digital, skeletal, and other congenital anomalies includes trisomy 13, Meckel syndrome, focal dermal hypoplasia (Goltz syndrome), Waardenburg's recessive anophthalmia syndrome,[11] oculodento-osseous dysplasia,[12] and the cerebro-oculofacial syndrome.[13]

X-linked diseases featuring microphthalmia include the Lenz microphthalmia syndrome, focal dermal hypoplasia (Goltz syndrome), and Norrie's disease.[14] Goltz syndrome is characterized by linear regions of dermal atrophy that become progressively hyperpigmented, colobomatous microphthalmia, mucous membrane papillomas, and digital anomalies in the form of syndactyly, polydactyly, or oligodactyly; it is probably X-linked dominant and lethal in males. In Norrie's disease there is no true microphthalmia, but rather phthisis bulbi that develops secondary to chronic retinal nonattachment and retinal dysplasia. Twenty-five percent of these individuals are mentally retarded, and the disease can be confused with the Lenz microphthalmia syndrome if patients are first seen in their teens or 20s.

Colobomatous microphthalmia is also seen in the association characterized by coloboma; heart disease; atresia choanae; retarded growth

and development or central nervous system anomalies, or both; genital anomalies or hypogonadism, or both; and ear anomalies or deafness, or both (CHARGE association).[15] None of our patients had choanal atresia or congenital heart disease, and digital anomalies are not characteristic of this association. The CHARGE association probably encompasses a clinically and genetically heterogeneous group of patients with microphthalmia and other congenital malformations. It is probably the most difficult entity to differentiate from the Lenz syndrome. Colobomatous microphthalmia and anal atresia are seen in the cat-eye syndrome[16]; however, patients with that syndrome do not have digital anomalies and most patients have an extra short acrocentric chromosome; our Patient 2 had a normal karyotype and severe malformations of the fingers and toes.

From the 12 cases that we included in Table 1 and the family studies in the three familial reports, it appears that the syndrome is inherited in an X-linked recessive fashion. There may be other affected maternal male relatives of our Patient 1, but they were not available for direct examination. There is variable manifestation of the different clinical traits in the Lenz syndrome.[7] Microphthalmos can range from mild, as in our Patient 1, to complete absence of the globe or anophthalmos, as in the cases reported by Hoefnagel, Keenan, and Allen.[2] The microphthalmos can be colobomatous (eight of 12 cases) or noncolobomatous (two of 12 cases) and is usually bilateral and asymmetric. Blepharoptosis was seen in nine patients (75%) and may not be related to the underlying small size of the globe; in several of the reported cases there was absence or attenuation of the eyelid fold. Additionally, the eyelid fissure may be shortened horizontally, and epicanthal folds may be present. To the best of our knowledge, our Patient 2 is the first patient with the Lenz syndrome to have had a documented retinal detachment and lens subluxation in the absence of a history of trauma or child abuse. Retinal detachment has been reported in eyes with chorioretinal colobomas and is thought to be the result of retinal breaks in the thinned junction between colobomatous and noncolobomatous areas.[17]

External ear abnormalities, present in ten patients (83%), characteristically took the form of hypoplasia of the antihelices and thinning and protrusion of the earlobes from the head; however, the ears may be hypoplastic, as in our Patient 2. Hearing impairment, as in our Patient 2, has not been previously reported, but most patients who have been described have not undergone audiologic examination. A high-arched palate or a cleft lip and palate was present in four patients. Dental anomalies, such as crowded teeth and widely spaced teeth, were seen in eight patients, as opposed to abnormal enamel formation in oculodentodigital dysplasia,[12] and the peg-shaped and small teeth in Goltz syndrome.

Skeletal anomalies (excluding digital anomalies) were seen in eight patients and were most prominent in the thoracic cage and spine. Sloping shoulders, barrel-chest, kyphoscoliosis, or gibbus deformities may be present. Thinning of the lateral third of the clavicle is a particular feature in some patients. Microcephaly was present in ten patients (83%). Developmental retardation seemed to be a universal finding and varied from mild to profound. Digital anomalies were present in seven of the 12 patients (58%), and were absent in the families described by Hoefnagel, Keenan, and Allen[2] and Goldberg and McKusick,[3] and in the patient described by Baraitser, Winter, and Taylor.[6] Syndactyly, clinodactyly, camptodactyly, and anomalies of the thumb (duplication or hypoplasia) can be seen. In Lenz's original report, the proband had clinodactyly and an affected relative had duplication of the thumb, indicating that both types of anomalies can coexist in the same family. Some patients may have a combination of the various digital anomalies. Both fingers and toes may be abnormal. Clinically evident congenital heart disease is not a feature of the syndrome; the only cardiac abnormality noted in this group of patients was mitral valve prolapse in the patient described by Pallota.[8] However, the autopsy on Lenz's original patient disclosed a bicuspid aortic valve and mild coarctation of the aorta. Urogenital anomalies in the form of cryptorchidism, renal hypoplasia, and renal aplasia were present in six patients; however, radiologic examination of the urinary system has not been performed on all patients and this figure may be an underestimate. Occasional findings include imperforate anus and hearing loss (Patient 2), spastic diplegia, sacral pits, webbed neck, and abnormal dermatoglyphs. Chromosomal studies have been performed in five of the 12 patients and the results were normal. Carrier mothers may have digital anomalies,[1,5] microcephaly,[5] and short stature.

The prominent features of the Lenz dysmorphogenetic syndrome are X-linked in-

TABLE 2
FREQUENCY OF MAJOR ABNORMALITIES IN 12 PATIENTS WITH THE LENZ MICROPHTHALMIA SYNDROME

ABNORMALITY	FREQUENCY NO.	(%)
Microphthalmia	12	(100)
Retardation	11	(92)
Ear abnormalities	10	(83)
Microcephaly	10	(83)
Blepharoptosis	9	(75)
Skeletal anomalies	8	(67)
Dental anomalies	8	(67)
Digital anomalies	7	(58)
Urogenital anomalies	6	(50)
Cleft lip/palate	4	(33)
Other	Rare	

heritance, microphthalmos, external ear abnormalities, microcephaly, developmental retardation, dental anomalies, digital anomalies, other skeletal malformations, and urogenital abnormalities (Table 2). Less common findings include cleft lip and palate abnormalities, hearing loss, congenital heart disease, and other rarer findings. The diagnosis should be suspected in male infants with microphthalmos and multiple congenital abnormalities, especially digital malformations which help differentiate the Lenz syndrome from other disease entities featuring microphthalmia.

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Cosegregation of X-Linked Retinitis Pigmentosa and Hemophilia A

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We examined a family pedigree in which retinitis pigmentosa and hemophilia A were inherited in an X-linked manner. Six female carriers were identified by electroretinography. Results of ophthalmoscopic examination were normal in two women, while four displayed marked variability in phenotypic expression. Six of seven males identified with retinitis pigmentosa had hemophilia A. One asymptomatic boy had a markedly abnormal electroretinogram despite normal ophthalmoscopic examination. Pedigree analysis showed a high recombination rate, which would be expected as these two genes are known to be at opposite arms of the X chromosome.

X-LINKED RETINITIS PIGMENTOSA is a rapidly progressive variant of retinitis pigmentosa in which young males may be severely affected early in life. Recognition of the carrier state in "silent" female relatives is critical to the diagnosis. The heterozygous carrier may be asymptomatic with good visual acuity, have normal dark adaptation thresholds, and have full visual fields, which compounds the difficulty in making the diagnosis.[1-7] The presence of a cylindrical refractive error of +1.50 diopter or greater in at-risk females may suggest the carrier state.[8] Indirect ophthalmoscopy may disclose features suggestive of the carrier state, such as isolated patches of bone spicules, subtle retinal pigment epithelial changes accompanied by corresponding visual field defects, or a tapetal-like reflex in the macula or perimacula.[4-10] The electroretinogram is an essential diagnostic tool in the detection of X-linked retinitis pigmentosa carriers, particularly in carriers who have little or no detectable fundus abnormality. Berson, Rosen, and Simonoff[11] showed that 96% of obligate X-linked retinitis pigmentosa carriers had a reduced amplitude to white light or delay in cone b-wave implicit times when full-field electroretinograms were performed on patients dark-adapted for 45 minutes. Using similar techniques, Fishman, Weinberg, and McMahon[8] were able to detect 86% of the carriers in their series.

Recently, it has been shown that individuals with X-linked retinitis pigmentosa demonstrating polymorphism with respect to locus L1.28 can be detected by linkage analysis with 86% confidence.[12,13] This approaches the diagnostic accuracy reported for the electroretinogram in all families. Current research is aimed at defining a marker that would detect 100% of individuals at risk in all families with X-linked retinitis pigmentosa. Further linkage analysis on suitable families needs to be performed to achieve this goal. This family with hemophilia A and X-linked retinitis pigmentosa presents an opportunity to perform such analyses.

Patients and Methods

The propositus, a 6-year-old boy (A-IV-8), with mild hemophilia A (factor VIII level of 14%), was referred to the Ophthalmology Clinic because of night blindness. A family pedigree was constructed from the information

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given by his mother, family members, and various physicians involved in the care of the family and from information obtained from the Hemophilia Clinic at our institution. Informed consent was obtained and family members were brought to the clinic for extensive examination. This included a thorough history and medical and ocular examinations, including best corrected visual acuity, cycloplegic refraction and retinoscopy, visual fields using Goldmann perimeter size V-4E white target and smaller targets, and dilated direct and indirect ophthalmoscopy. The following features were recorded: presence or absence of a tapetal reflex, irregularity of the fundus background caused by retinal pigment epithelial changes, and the presence or absence of pigment migration into the retina. Fundus photographs were obtained in all patients.

Binocular full-field electroretinograms were recorded after pupillary dilatation with tropicamide 1% and phenylephrine 2.5%, followed by dark adaptation for 45 minutes. The right ear electrode was used as a reference. The electrode leads were connected to an amplifier module and the amplifier was connected to a clinical averager. A stimulator was used to separate the rod and cone components. The stimulator contained a xenon flash tube with an energy output of 0.16 to 0.22 joules/flash. Single flashes of short wavelength, blue light, and low- and high-intensity white light were presented at two-second intervals. The photopic flicker was recorded at 30 Hz. The blue light elicits a rod-isolated response, the white light (dark adapted) elicits a mixed cone-rod response, and the white 30-Hz flicker elicits a cone-isolated response. The analysis time was 200 msec. Six repetitions were recorded for flicker. The stimulus rate was 0.9 per second and 30.9 per second for flicker; duration was 100 μsec. Background illumination for dark- and light-adapted states was 0 and 10 foot-lamberts, respectively. The strobe intensity was 0.25 log unit (0.24 foot-lambert second) for blue and low-intensity white light and 1.25 log units (1.84 foot-lambert seconds) for high-intensity white light and flicker. Band pass filter was set at 1 to 1,500 Hz. Normal values for b-wave amplitude were 80 to 125 μV for dark-adapted blue light, 200 to 350 μV for dark-adapted high-intensity white light, and 50 to 125 μV for 30-Hz flicker. These low normal values compared to other reports in the literature reflect the low intensity of the light flash stimulus. Normal values for the b-wave implicit times (using the 30-Hz flicker) were 30 to 36 msec.

Factor VIII assays were performed by a one-stage assay based on the partial thromboplastin time as previously described.[14] Normal factor VIII levels for our laboratory were 50% to 150%.

Chromosomal analyses on several affected males and several females were performed using standard G-banding and Q-banding techniques on extended chromosomes to search for evidence of a familial X chromosome abnormality.[15,16]

Peripheral blood for linkage analysis was obtained on all patients examined. The T-cell subpopulation was separated according to techniques recorded by Bloom and David[17] and infected with the Epstein-Barr virus prepared QIMR line as described by Marks, Dikinson, and Pope,[18] and subcultures were frozen and stored for linkage studies.

Results

The family pedigree is shown in Figure 1 and the clinical features of the family members are summarized in Tables 1 and 2. Subject A-II-7, a 76-year-old man, the grandfather of the propositus, was thoroughly examined just before his death. There was no history of night blindness or visual disturbance on his side of the family (pedigree branches A and C). His visual acuity was 20/50, compatible with nuclear sclerosis. Results of ophthalmoscopy and electroretinography were normal. He had mild hemophilia with low factor VIII level (12.6%). Other family members in this generation who had hemophilia included two brothers (A-II-5 and A-II-6), and a maternal uncle (C-I-2), who had three affected grandsons (C-III-1, C-III-2, and C-III-3).

The maternal grandmother of the propositus (B-II-1) died at age 54 years. She was not examined. Her brother (B-II-3) was examined and found to have no visual deficit, nor did he recall night blindness or hemophilia on his side of the family.

In generation III of pedigree branches A and B, the two male subjects (A-III-2 and A-III-7) were not examined. Neither they nor their offspring had symptoms of hemophilia or night blindness. The five females in this generation were all carriers of X-linked retinitis pigmentosa and hemophilia A. Subjects A-III-1 and A-III-6 were obligate carriers of X-linked retini-

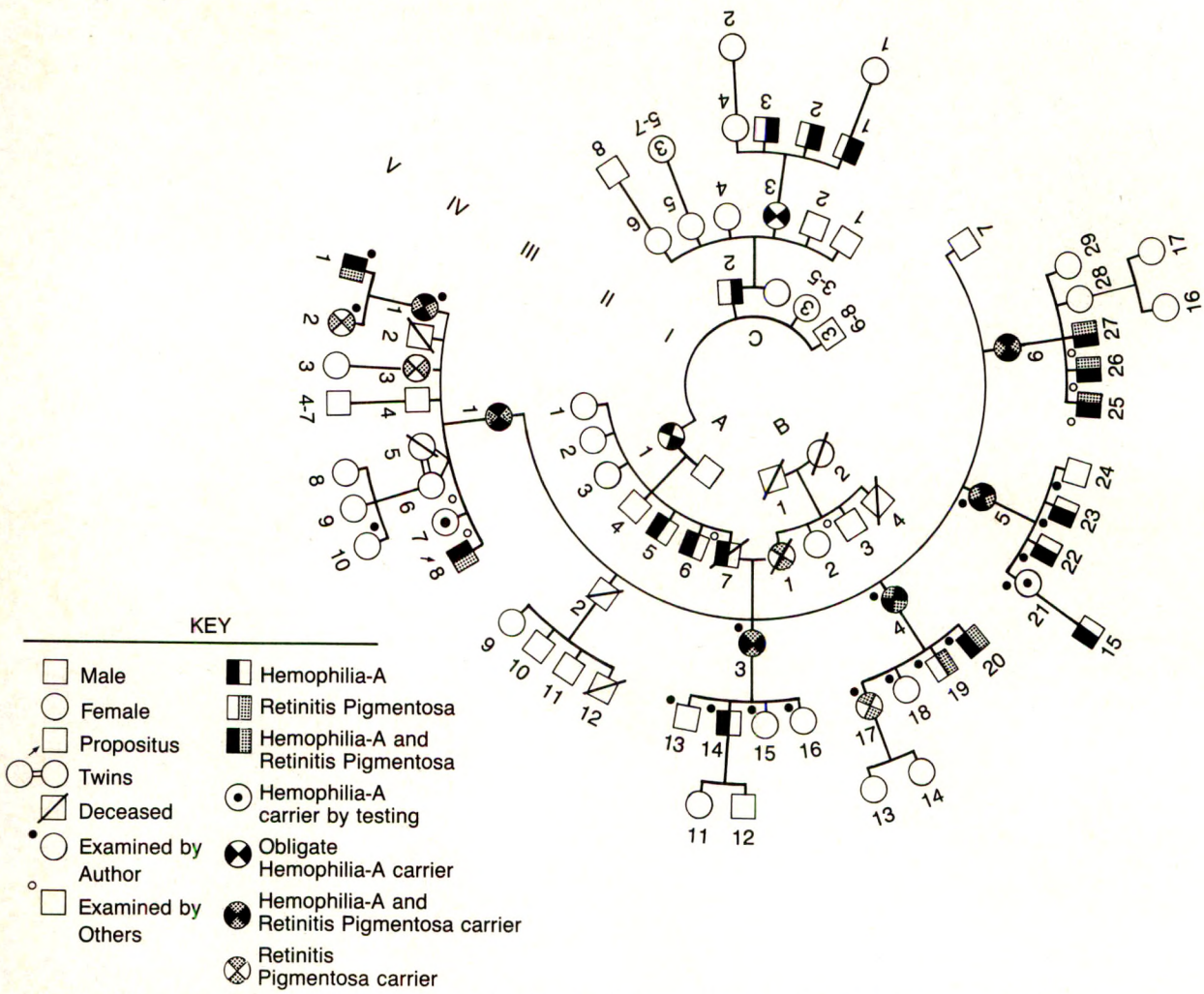


Fig. 1 (Rabinowitz and associates). X-linked retinitis pigmentosa and hemophilia A family pedigree.

tis pigmentosa, as they had affected offspring. Subjects A-III-3, A-III-4, and A-III-5 were identified as carriers of X-linked retinitis pigmentosa by electroretinography (Fig. 2). Ophthalmoscopic changes in Subjects A-III-3 and A-III-4 are shown in Figures 3 and 4. Subject A-III-5 was asymptomatic, with normal fundus findings, but had reduced b-wave amplitudes to blue and high-intensity white light stimuli in both eyes. Her best corrected visual acuity was 20/20 with a correction of R.E.: −3.00 +0.50 × 105 and L.E.: −3.00 +0.25 × 150.

Of the 12 females in generation A-IV, two carriers for X-linked retinitis pigmentosa were identified. Subject A-IV-1 (Fig. 5) is an obligate carrier for both X-linked retinitis pigmentosa and hemophilia, as her son has inherited both of these traits and her daughter has inherited at least one of them. Her electroretinographic findings confirm her carrier status for X-linked retinitis pigmentosa. Subject A-IV-17 was identified as a carrier by electroretinogram testing only, and Subject A-IV-3 has a history of nyctalopia and would require a more thorough examination to confirm the presence of retinitis pigmentosa. Subject A-IV-17 had normal visual acuity, with a correction of R.E.: −3.25 +1.75 × 180 and L.E.: −2.50 +1.75 × 180. Subjects A-IV-9, A-IV-28, and A-IV-29 were not examined. Of the 15 males in this generation, five had X-linked retinitis pigmentosa and hemophilia A (A-IV-8, A-IV-20, A-IV-25, A-IV-26,

TABLE 1
X-LINKED RETINITIS PIGMENTOSA CARRIERS DISPLAYING INTRAFAMILIAL VARIABILITY*

PEDIGREE NO.	AGE AT DIAGNOSIS (YRS)	BEST CORRECTED VISUAL ACUITY	REFRACTIVE ERROR	VISUAL FIELDS	OPHTHALMOSCOPIC FINDINGS	ELECTRORETINOGRAM B-WAVE AMPLITUDE
A-III-3	52	R.E.: 20/20 L.E.: 20/20	−0.75 sph −1.50 +0.50 × 90	Depressed superiorly	Retinal pigment epithelial degeneration inferiorly	Below normal
A-III-4	47	R.E.: 20/20 L.E.: 20/50	−1.25 sph −1.25 +3.25 × 90	Normal	Bone spicules along inferior arcades with attenuated arterioles in the right eye, left eye normal	Reduced 50%
A-IV-1	38	R.E.: 20/20 L.E.: 20/20	−12.00 +1.50 × 100 −11.00 +2.00 × 80	Depression corresponding to bone spicule pattern	Anomalous optic disks, bone spicule formation below inferior arcades	Reduced > 50%
A-V-2	18	R.E.: 20/20 L.E.: 20/20	−6.50 +0.50 × 90 −7.25 +2.25 × 90	Normal	Pigment in the vitreous, anomalous optic disks, areas of salt and pepper appearance to fundi	Reduced > 50%

*Tapetal reflex was absent in all patients. No patient had cataracts of any type. Patients A-III-3 and A-III-4 had minimal subjective night blindness. All patients were obligate hemophilia carriers, except patient A-V-2, who has not been tested.

and A-IV-27), and only one (A-IV-19) had X-linked retinitis pigmentosa only (Fig. 1). Their clinical findings are described in Table 2. Three asymptomatic males, Subjects A-IV-14, A-IV-22, and A-IV-23, had hemophilia A only, with normal findings on ocular examination. Subjects A-IV-2, A-IV-4, A-IV-10, and A-IV-11 were not examined and were presumed normal by history only. Subject A-IV-4 is at risk for being affected with hemophilia and needs to be tested.

In generation A-V, Subject A-V-1 had hemophilia and X-linked retinitis pigmentosa and Subject A-V-2 was identified as a carrier of X-linked retinitis pigmentosa by electroretinography (Tables 1 and 2, Fig. 6). Subject A-V-10 was normal; Subject A-V-15 had hemophilia A only. Other members of this generation have not yet been tested. Results of electroretinography of the heterozygous females tested are shown in Table 3. In Subject A-IV-3 we were unable to record cone b-wave amplitudes and implicit times because of technical difficulties. Sample electroretinograms of three carriers, Subjects A-III-3, A-III-4, and A-V-2, are shown in Figure 2. Sample electroretinograms of two affected males, Subjects A-V-1 and A-IV-25, are shown in Figure 7. Visual fields are described with clinical findings in Tables 1 and 2.

Chromosomal analysis on all patients tested showed no evidence of X chromosome abnormality.

Discussion

We were able to diagnose X-linked retinitis pigmentosa in this family through the detection of heterozygous carriers by indirect ophthalmoscopy and electroretinography. These observations allowed for the construction of an accurate family pedigree that clearly showed the absence of father-to-son transmission and the identification of carrier females. The pedigree supported an X-linked recessive mode of inheritance.

X-linked disease was further confirmed by the finding that only male subjects were severely affected with retinitis pigmentosa. Six men had findings typical of X-linked disease, including night blindness before 20 years of age,

TABLE 2
X-LINKED RETINITIS PIGMENTOSA AND HEMOPHILIA A (AFFECTED MALES)

PEDIGREE NO.	AGE AT DIAGNOSIS (YRS)	BEST CORRECTED VISUAL ACUITY	REFRACTIVE ERROR	VISUAL FIELD	ELECTRORETINOGRAM	SUBJECTIVE NIGHT BLINDNESS	OPHTHALMOSCOPIC FINDINGS	FACTOR VIII LEVEL† (%)
A-VI-8*	6	R.E.: 20/100 L.E.: 20/100	−3.50 +1.00 × 135 −4.00 +1.00 × 15	Not examined	Extinguished bilaterally	Present	Hypopigmented fundus with pigment migration in midperiphery	14
A-V-19	27	R.E.: 20/50 L.E.: 20/70	−12.25 +4.00 × 99 −11.24 +3.25 × 80	Constricted to 10 deg central island	Marked reduction	Present	Pale optic disks, narrowing of arterioles, and bone spicules in midperiphery	200
A-IV-20	13	R.E.: 20/30 L.E.: 20/30	−3.00 +0.50 × 130 −3.00 +0.50 × 50	Constricted to 10 deg central field	Not examined	Present	Cells in anterior vitreous, bone spicules in midperiphery, halo around maculae	14
A-IV-25	21	R.E.: 20/30 L.E.: 20/30	−2.25 +0.75 × 140 −3.00 +1.00 × 55	Ring scotomata	R.E.: depressed, L.E.: flat	Present	Early posterior subcapsular cataracts, pale optic disks, bone spicules in midperiphery	12
A-IV-26	16	R.E.: 20/30 L.E.: 20/30	−1.25 +0.75 × 140 −1.50 +2.25 × 95	Marked contraction with ring scotomata	Not examined	Absent	Vitreous band, gliosis of optic disks, mid-peripheral bone spicules, beaten copper appearance to maculae	13
A-IV-27	9	R.E.: 20/30 L.E.: 20/30	−2.75 +0.50 × 180 −4.00 sph	Minimal constriction with annular scotomata	Not examined	Present	Pigment in vitreous, midperipheral bone spicules, beaten copper appearance to maculae	9
A-V-1	14	R.E.: 20/30 L.E.: 20/30	−0.50 +0.50 × 90 −0.50 +0.75 × 90	Marked constriction	Depressed by 75%	Absent	Lens, disks, fundi normal	13

*Propositus.
†Normal level, 50% to 150%.

early decrease in visual acuity, and myopic astigmatism.[19,20] Although their fundi displayed marked variation in expression, most had characteristics typical of retinitis pigmentosa. Establishing an X-linked mode of inheritance was critical for providing a prognosis for these subjects. X-linked retinitis pigmentosa is rapidly progressive, with visual acuity dropping to 20/200 by age 30 years and possible blindness by age 40 years.[20]

The importance of performing electroretinograms on young, asymptomatic, at-risk males

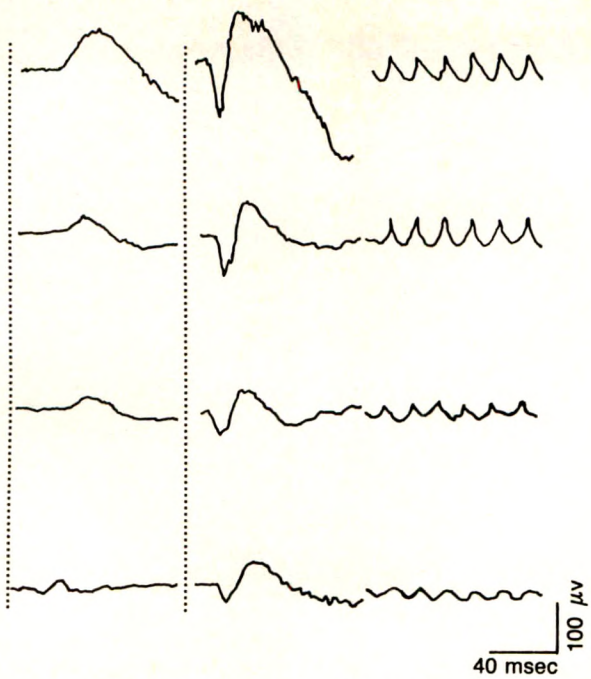


Fig. 2 (Rabinowitz and associates). Electroretinogram responses for a normal subject (top tracing) and three female carriers for X-linked retinitis pigmentosa, which illustrate depression of b-wave amplitudes. Corneal positivity is an upward deflection. Responses were obtained after 45 minutes of dark adaptation to single flashes of blue light (left column) and white light (middle column). Responses (right column) were obtained to 30-cps white light. Second tracing from top, Subject A-III-3; second tracing from bottom, Subject A-III-4; and bottom tracing, Subject A-V-2.

is illustrated by our findings in Subject A-V-1, a 14-year-old boy, who had bilaterally severely depressed electroretinograms in the absence of any symptoms. In families with retinitis pigmentosa, children or grandchildren of affected patients have been detected on the basis of reduced and delayed electroretinograms as early as 1 or 2 years of age. Electroretinograms can be used not only to identify which patients are affected, but also to establish which patients are normal. Berson[21] reported that patients 6 years of age or older with normal cone and rod amplitudes and normal cone and rod b-wave implicit times will not develop primary retinitis pigmentosa later in life.

Presence of a refractive cylinder of +1.50 diopter or greater in one eye was noted in four of six carriers in this family. Fishman, Weinberg, and McMahon[8] found similar changes in 78% of their patients and suggested that such a finding appreciably enhances the index of suspicion of the carrier state of X-linked retinitis pigmentosa.

Four of the six carriers had fundus findings consistent with the carrier state on indirect ophthalmoscopy. Subject A-III-3 had findings similar to those described by Bird[7] and Jay and Bird.[9] These included a subtle retinal pigment epithelial disturbance in the periphery inferiorly, with corresponding superior visual field depression. Two carriers had normal-appearing fundi and were designated as carriers on the basis of the electroretinographic findings alone. However, there may be up to a 14% error rate in detecting carriers by electroretinography only.[8]

The marked variability with respect to phenotypic expression of the X-linked heterozygote noted in our patients has been described previously.[7,9] Partial manifestation in female carriers, resulting in wide intrafamilial variation in this family, is best explained by the Lyon hypothesis[22]: early and random inactivation of one X chromosome leading to unmodified expression of the X-linked retinitis pigmentosa allele in a proportion of retinal cells.

There is also well-accepted interfamilial variation in heterozygous females. X-linked retinitis pigmentosa is thought to occur in three clinically distinguishable variants: the classic form, a type known as choroidoretinal dystrophy, and a variant form with a golden metallic or "tapetal" reflex in the heterozygous individual.[23,24] Controversy exists as to whether these phenotypic differences are the result of clinical variability in disease expression, heterogeneity in disease alleles at a single locus, or a multiplicity of loci for X-linked retinitis pigmentosa. Nussbaum and associates[25] studied a family in which heterozygous carriers demonstrated a tapetal-like reflex or "metallic sheen." They presented evidence which suggested that there may be a different locus distal to L1.28 on the short arm of the X chromosome for this particular variant. Our family does not fall into this category, as we were unable to document a tapetal reflex in any of the female carriers.

The depressed b-wave to high-intensity white stimulus on electroretinography was noted in all six carriers identified, making this the most consistent abnormal finding. Cone b-wave implicit times to a 30-Hz flicker stimulus was delayed in two patients who also had depressed b-wave amplitudes. Asymmetry of electroretinogram amplitudes between the two

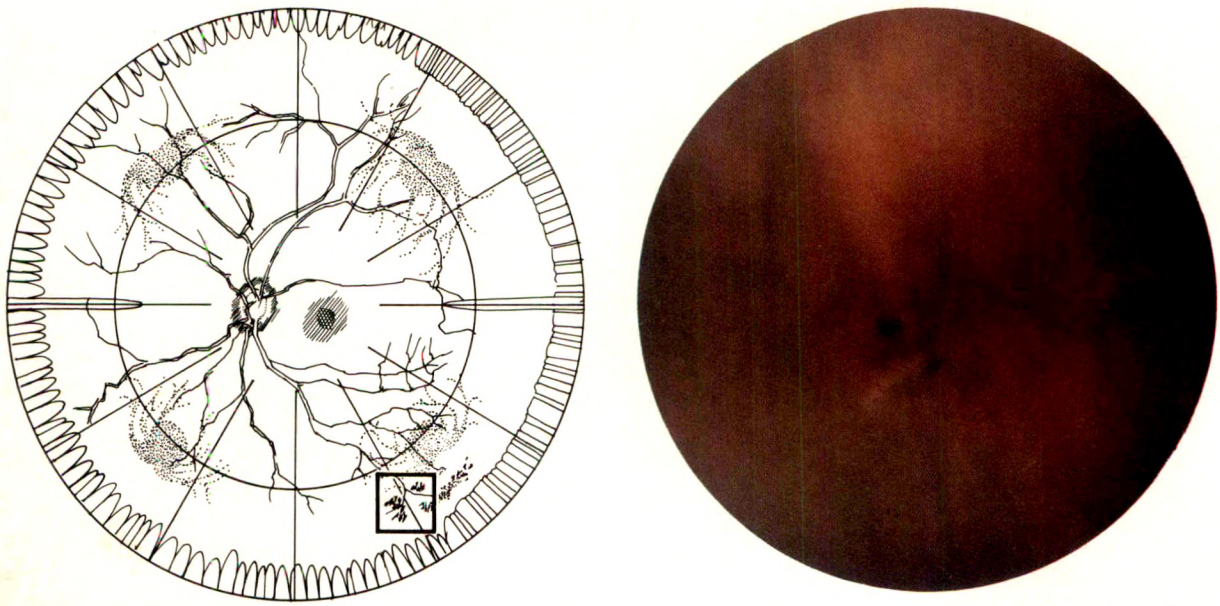


Fig. 3 (Rabinowitz and associates). Left eye, Subject A-III-3, a 52-year-old female carrier. Left, Fundus illustration. Right, Note peripheral degenerative changes in the far periphery inferiorly. She had corresponding superior visual field defects.

eyes and lack of correlation with fundus findings emphasizes the need to test both eyes when examining a suspected carrier. We did not find any carriers who had a prolonged cone implicit time to a 30-Hz flicker stimulus as an isolated abnormality, with normal cone and rod amplitudes, as noted by Berson, Rosen, and Simonoff[11] in a few of their carriers.

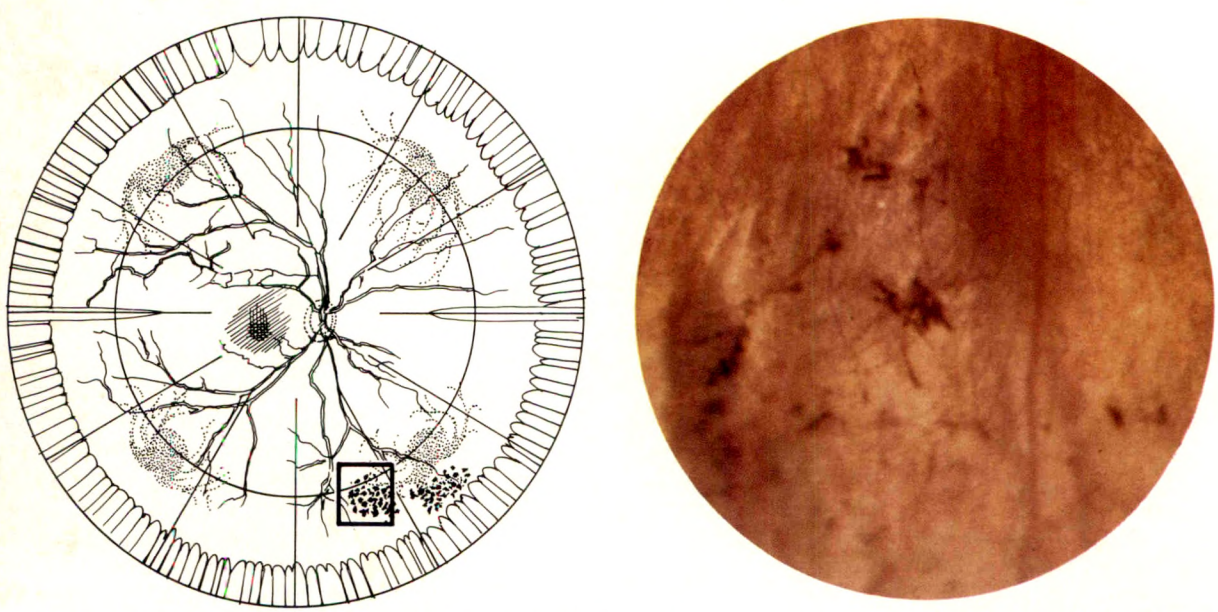


Fig. 4 (Rabinowitz and associates). Right eye, Subject A-III-4, a 47-year-old female carrier. Left, Fundus illustration. Right, Note bone spicules in the inferonasal periphery. Electroretinogram b-wave amplitude was depressed.

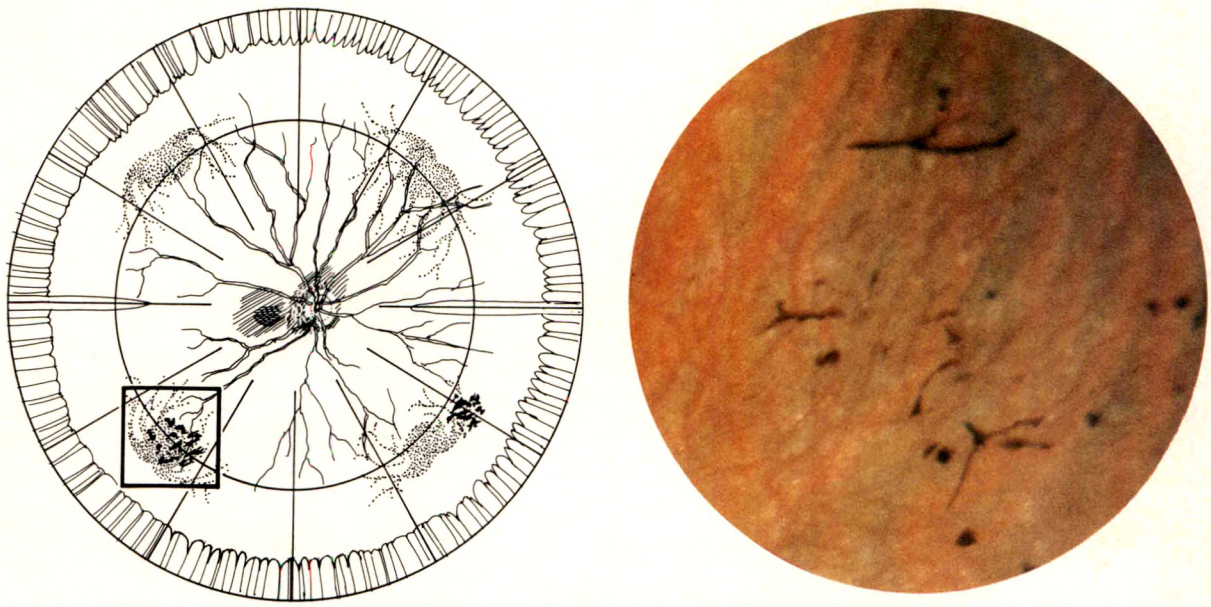


Fig. 5 (Rabinowitz and associates). Right eye, Subject A-IV-1, a 38 year-old asymptomatic female carrier. Left, Fundus illustration. Right, Note bone spicules inferior to the inferotemporal arcades.

Pedigree analysis—The gene for hemophilia A in this family can be traced back to the obligate carrier, Subject A-I-1. She had three affected sons, including Subject A-II-7, the grandfather of the propositus. The gene for X-linked retinitis pigmentosa was traced back to Subject B-II-1, the wife of A-II-7. Her lack of symptoms and subsequent family history are consistent with the carrier state for retinitis pigmentosa. All five daughters of this couple in

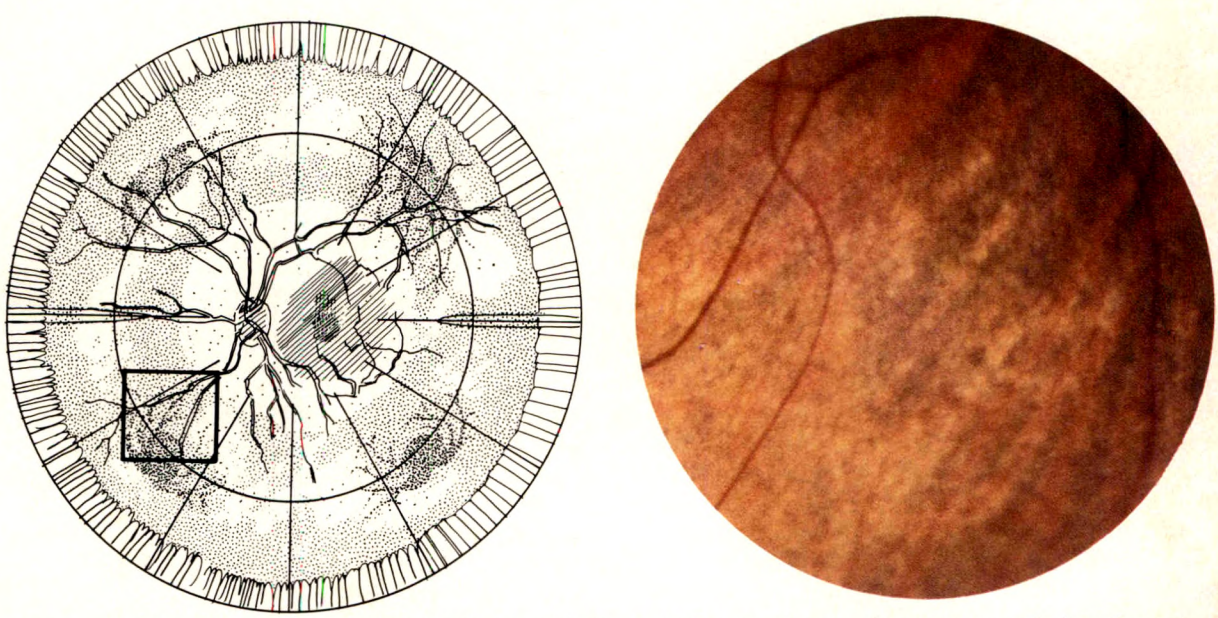


Fig. 6 (Rabinowitz and associates). Right eye of Subject A-V-2, an 18-year-old asymptomatic female carrier. Left, Fundus illustration. Right, Note scattered areas of salt and pepper appearance in the midperiphery accompanied by pigment throughout the vitreous.

TABLE 3
RESULTS OF ELECTRORETINOGRAM TO DETECT X-LINKED RETINITIS PIGMENTOSA HETEROZYGOUS CARRIERS

PEDIGREE NO.	AGE (YRS)	FUNDI* R.E.	FUNDI* L.E.	ELECTRORETINOGRAMS RIGHT EYE BLUE (μV)	RIGHT EYE WHITE (μV)	RIGHT EYE WHITE 30 Hz (μV)	RIGHT EYE IMPLICIT TIMES (MSEC)	LEFT EYE BLUE (μV)	LEFT EYE WHITE (μV)	LEFT EYE WHITE 30 Hz (μV)	LEFT EYE IMPLICIT TIMES (MSEC)
Carriers Detected											
A-III-3	52	PD	PD	80	156	104	38	70	156	100	36
A-III-4	47	B	N	48	118	72	34	52	147	80	34
A-III-5	54	N	N	64	92	72	32	68	64	68	32
A-IV-1	38	B	B	62	116	—	—	42	116	—	—
A-IV-17	28	N	N	76	128	84	34	76	128	80	34
A-V-2	18	SP	SP	36	104	32	42	32	100	32	40
Normal Females											
A-IV-7	28	N	N	156	336	80	32	124	332	88	32
A-IV-15	27	N	N	128	246	56	30	136	246	60	30
A-IV-16	13	N	N	148	256	80	32	148	256	80	32
A-IV-18	27	N	N	96	232	88	34	104	232	88	34

*PD, peripheral degeneration; B, bone spicules; N, normal; SP, salt and pepper appearance.

generation A-III are obligate carriers of hemophilia A, and it is remarkable that each also inherited the X chromosome for X-linked retinitis pigmentosa from their mother (B-II-1) (probability, $1/2^5$).

The five male subjects in generation A-IV who expressed X-linked retinitis pigmentosa and hemophilia A represent recombinants. The high recombination rate is not surprising, considering the genes for X-linked retinitis pigmentosa and hemophilia A are known to be at opposite ends of the X chromosome (XLRP:Xp 11.3RPX; Heme A Xq 28).[26,27] Subject A-IV-19 was the only male with isolated retinitis pigmentosa; other males (Subjects A-IV-14, A-IV-22, A-IV-23, and A-V-15) expressed only hemophilia A. Subject A-IV-1 must also represent a recombination event since she could only receive one X chromosome from her mother; her son, Subject A-V-1, has both X-linked traits. The husband of Subject A-IV-1 was normal. However, her daughter, Subject A-V-2, must be yet another recombinant, as she showed only evidence of retinitis pigmentosa.

This family represents a unique occurrence of events. The frequency of the X-linked retinitis pigmentosa allele in the general population is 2.0×10^{-5}, based on the prevalence of X-linked retinitis pigmentosa in Maine.[28] The gene frequency for hemophilia A is generally accepted to be 1.0×10^{-4}, the incidence of the condition in males.[29] Based on the frequency of these alleles in the general population, the probability of two people meeting with these two separate genes is 2.0×10^{-9}.

With well-defined clinical findings to diagnose hemophilia A and retinitis pigmentosa, pedigree construction aids in establishing the mode of inheritance of these conditions either alone or in combination and allows the physician to provide family members with an estimation of risk and reproductive choices. In this family with mild hemophilia, prevention by prenatal diagnosis may rarely be elected. In X-linked retinitis pigmentosa, recent advances now allow options for families at risk. Linkage has been demonstrated between DNA probe L1.28 and the X-linked retinitis pigmentosa locus on the short arm of the X chromosome.[12] The use of this probe is limited by its distance from the X-linked retinitis pigmentosa gene (approximately 5 centimorgans) and by the fact that only 40% of kindreds show informative restriction fragment length polymorphism.[13] However, identification of other highly polymorphic markers flanking the X-linked retinitis

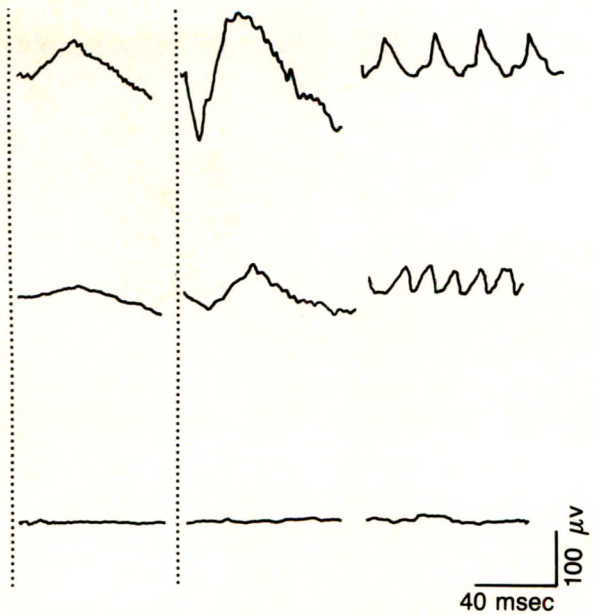


Fig. 7 (Rabinowitz and associates). Electroretinogram responses for a normal subject (top tracing) and two male patients with X-linked retinitis pigmentosa and hemophilia A, which demonstrate marked depression of all waves of the electroretinogram. Responses were obtained after 45 minutes of dark adaptation to single flashes of blue light (left column) and white light (middle column). Responses (right column) were obtained to 30-cps white light. Middle tracing, Subject A-V-1, a 14-year-old boy, had no fundus findings and was asymptomatic. Subject A-IV-25, a 21-year-old man, had severe retinitis pigmentosa with extensive fundus findings.

pigmentosa gene may allow a greater proportion of families to be informative for the DNA L1.28 probe or newer probes that are currently being developed.

ACKNOWLEDGMENT

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OPHTHALMIC MINIATURE

I wander all night in my vision,
Stepping with light feet, swiftly and noiselessly stepping and stopping,
Bending with open eyes over the shut eyes of sleepers,
Wandering and confused, lost to myself, ill-assorted, contradictory,
Pausing, gazing, bending, and stopping.

How solemn they look there, stretch'd and still,
How quiet they breathe, the little children in their cradles.

Walt Whitman, "The Sleepers" (1881)
Leaves of Grass and Selected Prose
New York, Holt, Rinehart and Winston, Inc., 1949, p. 349

The Surgical Treatment of Blepharoptosis in Oculomotor Nerve Palsy

Timothy J. Malone, M.D., and Jeffrey A. Nerad, M.D.

We reviewed retrospectively 170 cases of congenital and acquired oculomotor nerve palsy to determine the effectiveness of surgery in the treatment of blepharoptosis in oculomotor nerve palsy. Twenty patients had had surgical repair of the blepharoptosis. Patients with congenital oculomotor palsy were more often selected for blepharoptosis surgery than patients with acquired blepharoptosis because of the absence of diplopia caused by suppression in congenital cases. There was complete recovery in 72 of 109 patients (66%) with acquired oculomotor palsy. Results were judged with regard to functional improvement and cosmetic improvement. Primary functional disability was relieved by lifting the eyelid above the pupil in ten of 12 patients (83%). Primary cosmetic disability was relieved in six of six patients. Corneal complications occurred in six of 20 patients (30%) who were treated surgically.

THE SUCCESSFUL SURGICAL rehabilitation of patients with blepharoptosis caused by oculomotor nerve palsy depends on factors affecting patient selection, surgical expectations, and risks of complications. The neurologic characteristics of oculomotor nerve palsy restrict the selection of suitable candidates whose functional and cosmetic disability from blepharoptosis may benefit from carefully chosen surgical intervention.[1-4] The blepharoptosis surgeon must identify methods and goals for eyelid elevation that are realizable within the constraints of the neural disturbance. The degree of oculomotor paresis, whether partial or complete, restricts the expectations for ideal postsurgical ocular alignment and motility[5-7] of the strabismus surgeon in a similar manner. The associated presence of amblyopia, visual deficits, and involvement of other cranial nerves, particularly the trigeminal and facial nerves; capacity for binocular fusion; alternation of paretic and spastic function in cyclic oculomotor palsy[8-11]; and recovery with or without aberrant regeneration[12-17] further affect the selection of patients for and the successful outcome of blepharoptosis surgery in oculomotor nerve palsy. This study reflects the experience regarding the blepharoptosis of oculomotor nerve palsy over a 25-year period at our institution.

Subjects and Methods

In a survey of the records of patients examined at the University of Iowa Hospitals and Clinics, 170 patients were identified in whom oculomotor nerve palsy had been diagnosed. Each of these patients had been examined during the years 1961 through 1986 by members of the Department of Ophthalmology, including the Neuro-Ophthalmology Service, the Pediatric Ophthalmology and Strabismus Service, and the Oculoplastics and Orbital Service. The cases were reviewed to identify the incidence, results, and complications relating to blepharoptosis in oculomotor nerve palsy.

Results

Of the 170 patients identified, congenital oculomotor nerve palsy had been diagnosed in 27 (16%) and acquired oculomotor nerve palsy had been diagnosed in 143 (84%). Of 27 congenital cases, 24 (89%) were unilateral. Nineteen of these 27 patients (70%) had amblyopia, as measured by a difference in visual acuity of

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two or more Snellen chart lines, which was attributable to the ocular deviation or blepharoptosis of oculomotor nerve palsy. Two patients had typical cyclic oculomotor palsy. The paretic phase of exotropia, mydriasis, and blepharoptosis alternated with the spastic phase of oculomotor nerve function. In four variant cases of cyclic oculomotor palsy, only the eyelid and pupil cycled. With the eye resting in primary gaze position, a highly variable blepharoptosis was associated with a variable pupil size. The spastic phase was irregular, ranging from brief 3- to 4-second eyelid twitches to prolonged episodes of eyelid flutter.

Of 143 acquired cases, 135 (94%) were unilateral. Thirteen patients (9%) had reduced visual acuity. Four children, whose average age was 3.5 years (range, 16 months to 6 years), became amblyopic after the onset of oculomotor nerve palsy. There were four adult patients with traumatic optic neuropathy, and four adults with compressive optic neuropathy caused by tumor or aneurysm. One adult patient had optic neuritis from multiple sclerosis.

Ischemia was the most common cause of acquired oculomotor nerve palsy (Table 1) and was associated with diabetes mellitus, systemic hypertension, atherosclerosis, or ophthalmoplegic migraine (two cases). When performed, results of the examination for intracranial aneurysm or tumor were negative. In cases of ischemia, no aberrant regeneration after recovery was noted. Of the 28 cases of oculomotor nerve palsy caused by aneurysm, there were four cases of subarachnoid hemorrhage. Of the 15 cases caused by tumor, there were six cases of pituitary adenoma, two cases each of lymphoma and metastatic breast carcinoma, and one case each of medulloblastoma, craniopharyngioma, nasopharyngioma, metastatic renal cell carcinoma, and cavernous sinus hemangioma. Of the six cases caused by inflammation or infection, there were two cases of meningitis, and one case each of orbital abscess, orbital pseudotumor, multiple sclerosis, and Tolosa Hunt syndrome.

TABLE 1
CAUSE OF ACQUIRED OCULOMOTOR PALSY
(N = 143)

CAUSE	NO. OF CASES	%
Ischemia	51	36
Trauma	34	24
Aneurysm	28	20
Tumor	15	10
Undetermined	9	6
Inflammatory/infectious	6	4

Of the 143 patients with acquired oculomotor nerve palsy, 14 never had blepharoptosis, indicating that the superior division of the oculomotor nerve was spared. Twenty-three patients had 2 to 3 mm of blepharoptosis, and 14 had greater than or equal to 4 mm of blepharoptosis (Table 2). There was no follow-up regarding recovery in 20 patients. Five of these patients died from tumor or subarachnoid hemorrhage.

Multiple measurements were taken in 109 patients with acquired oculomotor nerve palsy who had blepharoptosis. The remaining blepharoptosis after any recovery was considered stable when eyelid fissure size was unchanged on two or more visits at least one year after onset of the deficit. Complete recovery, 0 to 1 mm of residual stable blepharoptosis, was noted in 72 of these 109 patients (66%). Thirty-seven patients (34%) had 2 mm or more of residual blepharoptosis. In this group of 37 patients, blepharoptosis surgery was recommended to ten patients (27%) and was performed in five (14%).

Aberrant regeneration—Two synkinetic patterns affecting eyelid movement were reliably recorded by examiners: eyelid elevation on attempted downgaze (pseudo-Graefe sign) and eyelid elevation on attempted adduction. The pseudo-Graefe sign was present in three of 27 congenital cases (11%) and in 16 of 92 nonischemic acquired cases (17%). Eyelid elevation on attempted adduction was present in six of 27 congenital cases (22%) and in 16 of 92 nonischemic acquired cases (17%). One or both patterns of eyelid synkinesis may have been present simultaneously.

Patient selection—Blepharoptosis surgery was performed on 20 patients. Fifteen patients (75%) had congenital oculomotor nerve palsy, and five (25%) had acquired oculomotor nerve palsy. Surgery was performed elsewhere on two of the 20 patients, and preoperative measurements were unavailable.

The amount of blepharoptosis averaged 3.6 mm in congenital cases and 5.3 mm in acquired cases. Excluded from these averages were the two previously operated on patients and four patients with congenital oculomotor nerve palsy who had variable blepharoptosis because of cyclic spasms or aberrant regeneration.

Visual acuity was decreased in 14 of 20 eyes (70%) undergoing blepharoptosis repair. In thirteen of the 15 congenital cases (87%), the

TABLE 2
RECOVERY IN ACQUIRED OCULOMOTOR PALSY

CAUSE	NO. OF CASES	RESIDUAL BLEPHAROPTOSIS AFTER 1 YEAR			NO BLEPHAROPTOSIS EVER PRESENT	INADEQUATE FOLLOW-UP
		0–1 MM BLEPHAROPTOSIS	2–3 MM BLEPHAROPTOSIS	≥ 4 MM BLEPHAROPTOSIS		
Ischemia	51	39	4	0	1	7
Trauma	34	14	7*	4†	6	3
Aneurysm	28	10	5‡	3	4	6 (2 patients died)
Tumor	15	3	3	6§	0	3 (3 patients died)
Undetermined	9	2	3	1	2	1
Inflammatory/ infectious	6	4	1	0	1	0
Total	143	72	23	14	14	20

*Surgery performed in two patients.

†Surgery recommended in all four patients.

‡Surgery recommended in one patient.

§Surgery performed in three patients.

patients had amblyopia. In one of five acquired cases, the patient had traumatic optic neuropathy, reducing visual acuity to 20/50 compared to 20/20 in the uninvolved eye. In two patients, however, the blepharoptotic eyelid covered the patient's only eye with good central acuity.

In the 15 congenital cases, diplopia was avoided by suppression in 14 patients. Fusion was obtained with an assumed head position in one congenital case and three acquired cases. Of two remaining acquired cases, one patient had single binocular vision in primary gaze position, and one patient was diplopic and fused with prisms with some difficulty. All 20 patients underwent strabismus surgery,[6] either before or in combination with blepharoptosis surgery.

The average interval between onset of acquired oculomotor palsy and surgery was 25 months (range, 16 to 36 months). To insure that surgical correction is performed on the residual stable blepharoptosis and that maximal recovery has occurred, a delay of surgery for one year after traumatic oculomotor palsy has been proposed.[18]

Blepharoptosis surgery was not recommended to other patients for a variety of reasons, both subjective and objective, including patient disinterest in cosmesis, reduced visual acuity of the involved eye, persistent diplopia, absent corneal sensation, and inadequate delay after onset of acquired oculomotor nerve palsy.

Surgical expectations and technique—Levator muscle function primarily determined the choice of surgical approach. Four patients with no measurable levator muscle function underwent frontalis sling procedures. The average levator muscle function of the remaining 16 patients was 7.6 mm (range, 2.5 to 15 mm); each underwent levator muscle surgery, either levator muscle resection or aponeurosis advancement. One patient with poor levator muscle function (2.5 mm) refused a frontalis sling procedure and underwent a Whitnall's sling operation.

The surgical expectations and results were assessed retrospectively based on whether the blepharoptosis procedure corrected the primary disability, either functionally or cosmetically. To separate the functional disability from the cosmetic disability of blepharoptosis, the patients were divided into two groups according to preoperative fissure size. Fissure size of less than 5 mm was assumed to produce primarily a functional disability by occluding the pupil. Fissure size greater than 5 mm was assumed to allow a more adequate visual field and to produce primarily a cosmetic disability.

Of 12 patients with a preoperative fissure size of less than 5 mm, an assumed functional disability, ten patients achieved postoperative fissures of at least 5 mm (average, 6.9 mm; range, 5 to 10 mm) (Table 3). Of seven patients with complete blepharoptosis (Fig. 1), postop-

TABLE 3
RESULTS OF BLEPHAROPTOSIS SURGERY FOR PRIMARY FUNCTIONAL DISABILITY

PREOPERATIVE FISSURE < 5 MM (R.E./L.E.) (MM)	POSTOPERATIVE FISSURE (R.E./L.E.) (MM)
2/7	5/7
11/0-4	13/10
0-3/11	5/10
0/9	5/10
0/10	6/10
2/8	3.5/8
4/9	5.5/9
8/4.5	9/8
4/8	5/8
8/4	8/5.5
3/8	10/10
12/2	12/9

erative fissures were greater than 5 mm in all but one patient. Two patients had unsatisfactory postoperative eyelid elevation.

Of six patients with a preoperative fissure greater than 5 mm, an assumed primarily cosmetic disability since the pupil was not occluded, all achieved a postoperative fissure difference of 0 to 1 mm (Table 4), which improved cosmetic symmetry (Fig. 2).

The presence of variable blepharoptosis caused by cyclic oculomotor palsy or synkinesis of aberrant regeneration may affect the choice of surgical approach. Four patients with cyclic oculomotor palsy underwent blepharoptosis surgery. The cyclic function of the anomalously innervated levator muscle was eliminated in two cases. One patient underwent a bilateral frontalis sling procedure with bilateral levator muscle myectomy as described by Dillman and Anderson.[19] Another patient with unilateral cyclic oculomotor palsy and dense amblyopia underwent a unilateral frontalis sling procedure with homologous preserved fascia lata and levator muscle transposition to the superior orbital rim as described by Dryden, Fleming, and Quickert.[20] Neither patient exhibited postoperative eyelid cycling. Two patients with cyclic oculomotor palsy underwent levator muscle aponeurosis advancement, each of whom exhibited persistent postoperative eyelid cycling (Fig. 3).

TABLE 4
RESULTS OF BLEPHAROPTOSIS SURGERY FOR PRIMARY COSMETIC DISABILITY

PREOPERATIVE FISSURE >5 MM (R.E./L.E.) (MM)	POSTOPERATIVE FISSURE (R.E./L.E.) (MM)
6/10	10/10
7.5/11	10/11
6/9	8/9
9/6	9/8
7.5/10	10/10
11/8	11/11

Four patients with aberrant regeneration of oculomotor palsy and eyelid elevation on adduction or vertical gaze change had persistent synkinetic eyelid movements despite successful blepharoptosis repair (Fig. 4). No patient with aberrant regeneration in this series underwent levator muscle extirpation/transposition procedures.

In one case the eyelid height was adjusted intraoperatively to the patient's assumed head position of binocular fusion rather than primary gaze head position. An undercorrection resulted. The measured preoperative levator muscle function was not functionally available because of an apparent lack of synkinetic stimulation provided by this ocular position. In at least one other patient with aberrant regeneration, the significant levator muscle function, as traditionally determined by measuring the excursion from downgaze to upgaze, was overestimated. The apparent levator muscle function

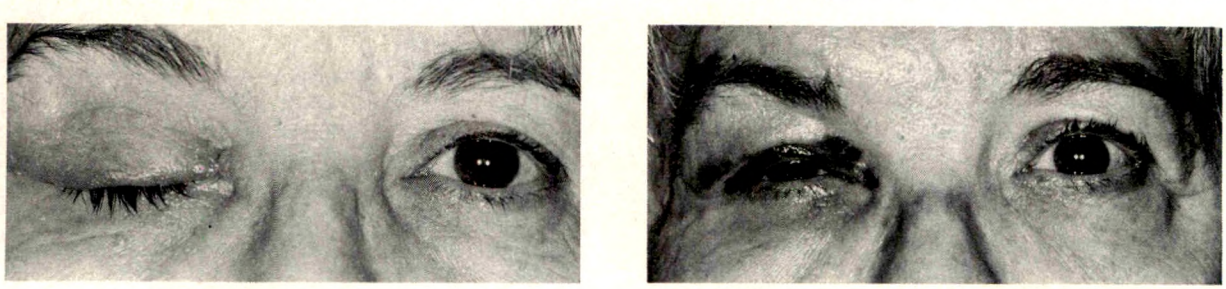


Fig. 1 (Malone and Nerad). Functional disability from complete blepharoptosis of right upper eyelid. Left, Preoperative appearance. Right, After unilateral frontalis sling procedure. Right eye fissure size, 5 mm.

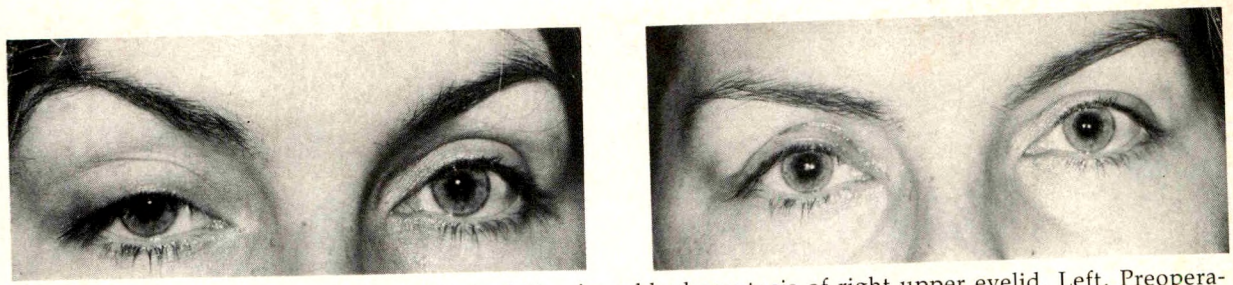


Fig. 2 (Malone and Nerad). Cosmetic disability from blepharoptosis of right upper eyelid. Left, Preoperatively, fissure size is R.E.: 7.5 mm and L.E.: 10 mm. Right, Postoperative levator muscle aponeurosis advancement of the right upper eyelid. Fissure size is 10 mm in both eyes.

was secondary to aberrant regeneration of the levator muscle from the superior rectus muscle. In patients with levator muscle function only in upgaze, levator muscle shortening will lead to an undercorrection.

Only one patient underwent reoperation. The patient's unilateral complete oculomotor palsy after resection of a pituitary adenoma was complicated by ipsilateral loss of eyebrow function. Furthermore, the contralateral eye suffered a loss of central vision as well as homonymous hemianopia. A conservative unilateral frontalis sling procedure to the paralytic eyebrow to allow monocular but split central fixation in the only seeing eye produced an acceptable eyelid height. Eventually the paralytic eyebrow became ptotic, causing the eyelid to drop. Direct eyebrowplasty with periosteal fixation allowed a 5-mm fissure size, with the eyelid bisecting the pupil (Fig. 5). Despite the absence of Bell's phenomenon, corneal exposure symptoms were alleviated after lower eyelid elevation using auricular cartilage as a spacer graft. A nighttime moisture chamber and lubricants provided additional safety.

Of the 20 cases of blepharoptosis treated surgically, six patients (30%) experienced corneal complications. Four of these patients developed corneal scars, and two had chronic punctate keratopathy without scarring. All six patients required the use of topical lubricants throughout the entire follow-up period (average, 6.6 years; range, 15 months to 12 years). These six patients were all undercorrected; the residual blepharoptosis averaged 3 mm (range, 1 to 5 mm). The absence of supraduction, Bell's phenomenon, and the degree of residual hypotropia (average, 10 prism diopters; range, 0 to 30 prism diopters) were not different from patients without corneal complications. The presence of lagophthalmos, corneal sensitivity, adequate tear function, and blink was not regularly recorded by examiners in this retrospective study. These factors were probably significant in the development of postoperative corneal complications. Indeed, individual pa-

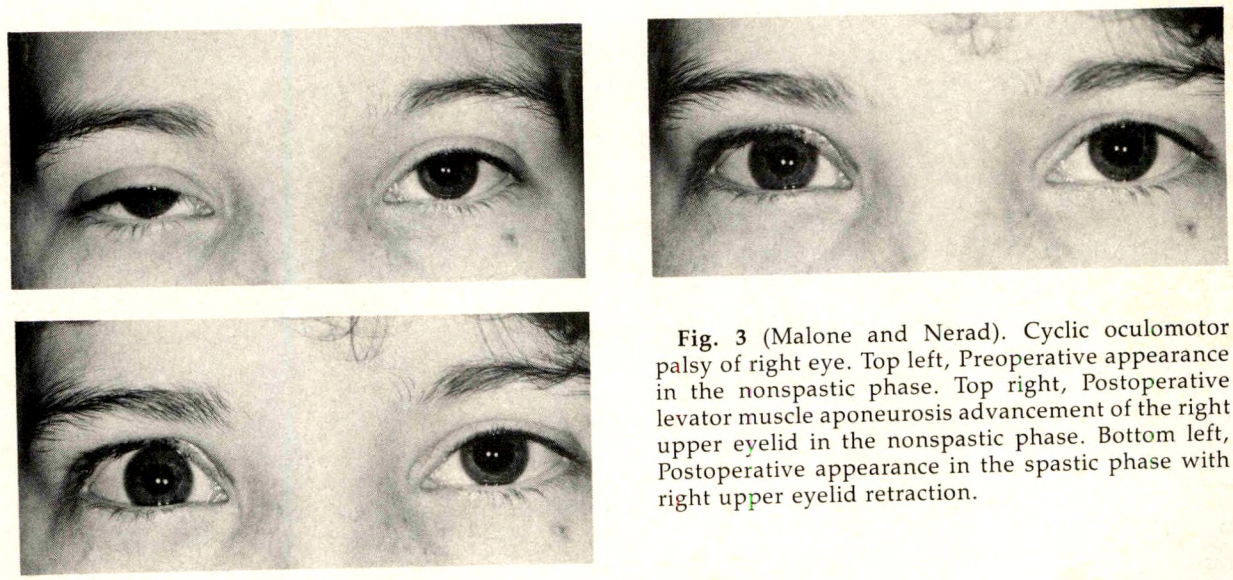


Fig. 3 (Malone and Nerad). Cyclic oculomotor palsy of right eye. Top left, Preoperative appearance in the nonspastic phase. Top right, Postoperative levator muscle aponeurosis advancement of the right upper eyelid in the nonspastic phase. Bottom left, Postoperative appearance in the spastic phase with right upper eyelid retraction.

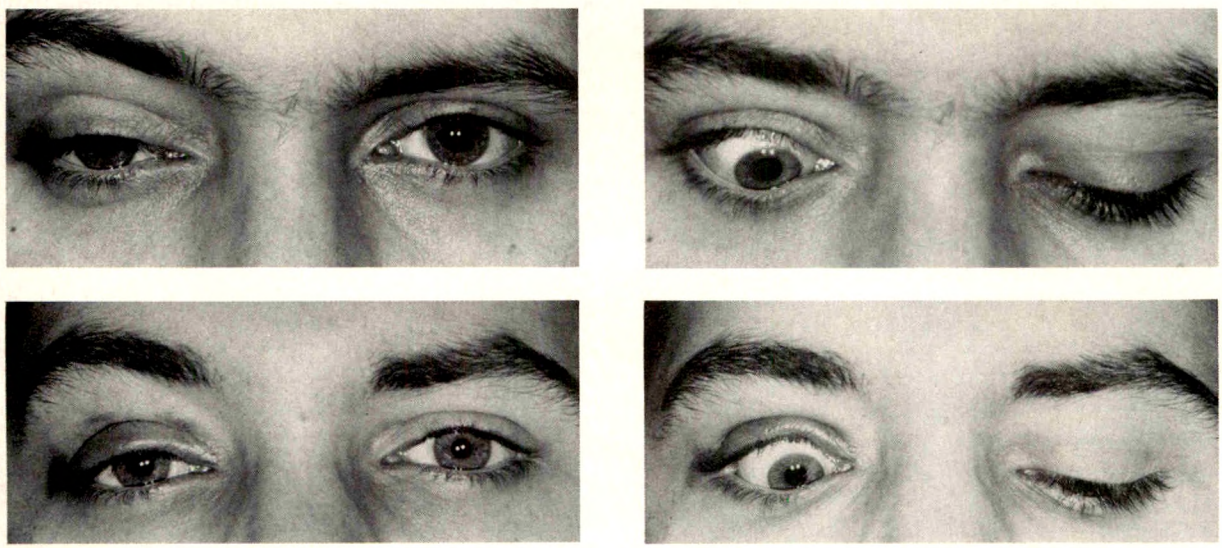


Fig. 4 (Malone and Nerad). Persistent synkinetic eyelid elevation on downgaze (pseudo-Graefe sign). Top left and right, Preoperative appearance in primary gaze and downgaze, respectively. Bottom left and right, Postoperative appearance after levator muscle aponeurosis advancement in primary gaze and downgaze.

tient compliance with ocular lubricant therapy was an intangible risk factor.

Other complications included one case each of eyelash ptosis, redundant eyelid fold, and irregular eyelid contour. There were no incidents of postoperative ectropion, entropion, infection, or hemorrhage.

Discussion

The blepharoptosis of oculomotor nerve palsy is often treated surgically in congenital cases but rarely so in acquired cases, as documented in this series. The blepharoptosis of congenital oculomotor nerve palsy is stable, nonprogressive, generally isolated, and rarely complicated by associated severe neurologic deficits found in acquired oculomotor nerve palsy.[21,22] The blepharoptosis of acquired oculomotor nerve palsy is treated surgically only after the neurologic deficit has stabilized. Any underlying systemic or intracranial process must be treated. In some cases, these underlying conditions are severe; in this series five patients died. However, most patients (67%) with acquired palsy had good to excellent recovery, leaving minimal or no residual blepharoptosis. This is related to the high prevalence of oculomotor nerve ischemia from diabetes mellitus and hypertension and the underlying neural capacity for resilience after incomplete insult.[12] Of the 72 patients with complete recovery of blepharoptosis, 39 (54%) had ischemic third nerve palsies. Of the 43 patients with ischemic third nerve palsy, 39 (90%) recovered.

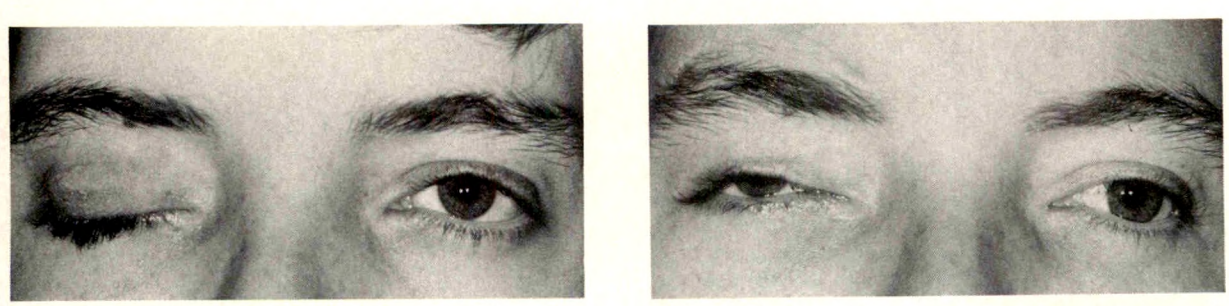


Fig. 5 (Malone and Nerad). Complete right oculomotor palsy, bilateral eyebrow paresis, split central visual field in the right eye, and no light perception in the left eye. Left, Preoperative appearance after strabismus surgery. Right, Postoperative frontalis sling of the right upper eyelid and direct right eyebrowplasty with periosteal fixation of the right eyebrow.

The visual and binocular status of the blepharoptotic patient determines to a great extent the select group for whom blepharoptosis surgery is advantageous. Patients with congenital oculomotor nerve palsy usually do not experience diplopia because of amblyopia or suppression. Patients with acquired oculomotor palsy often undergo multiple strabismus surgical procedures to achieve a limited field of single binocular vision.[5-7] When this is achieved, it is often maintained by a degree of assumed head position. Persistent diplopia may contraindicate blepharoptosis surgery in acquired oculomotor nerve palsy. Only one patient in this series had difficulty avoiding diplopia postoperatively.

The achievement of good cosmesis in primary gaze position must be measured against the degree of functional as compared to cosmetic disability, the presence and extent of bizarre synkinetic eyelid movements on attempted gaze shift, as well as the protection of the ocular surface from dessication in a relatively immobile globe. Additionally, cosmesis plays a large role in the choice between the unilateral or bilateral surgical approach in unilateral disease.

The division of the surgical indications into functional disability or cosmetic disability helps to define the appropriate expectations of surgery, and thus provides a measure of success for both the surgeon and the patient. In this study, patients with functional disability from severe blepharoptosis were successfully treated in ten of 12 cases with a fissure size greater than 5 mm postoperatively and the eyelid at least bisecting the pupil in these mildly hypotropic eyes (Table 3). Cosmetic intent for surgery, preoperative fissure size of greater than 5 mm, was undertaken less frequently in this series, but was successful in each case, as indicated by a postoperative fissure difference of 0 to 1 mm (Table 4).

The levator muscle was used for eyelid elevation in all cases with good levator muscle function. The levator muscle was approached anteriorly through the skin in all cases. Before 1976, the levator muscle was resected by the Berke technique.[23] The levator muscle aponeurosis advancement technique[24] has been used subsequently. Eyebrow suspension was used in cases of absent to poor levator muscle function and in cases of cyclic oculomotor palsy with absent levator muscle function in the paretic phase. Eyebrow suspension of the eyelid by frontalis muscle sling using autogenous or homologous fascia lata was performed by the Crawford technique,[25] its modification by Beard,[1] and its postseptal modification described by Patrinely and Anderson.[26]

Eight patients in this series had variable blepharoptosis as a result of either cyclic palsy (four patients) or aberrant regeneration (four patients). Surgery successfully treated the cyclic/synkinetic aspects in only two patients. Interruption of levator muscle function by myectomy[19] or transposition to the superior orbital rim[20] followed by eyebrow suspension was successful in eliminating the cyclic/synkinetic movements in both cases. The cosmetic blemish from residual cyclic and synkinetic eyelid behavior after blepharoptosis surgery without interruption of levator muscle action is demonstrated in Figures 3 and 4. A quantifiable approach to synkinetic disorders measuring millimeters of anomalous eyelid excursion would be valuable in sorting out the relative components of blepharoptosis and cyclic/synkinetic movements. The approach commonly taken was to perform levator muscle blepharoptosis surgery initially, with the possibility for levator muscle myectomy/eyebrow suspension[19] used only as a secondary procedure. None of the patients in this series who underwent a primary levator muscle blepharoptosis repair returned for secondary levator muscle myectomy/eyebrow suspension, although the abnormal movements persisted.

Exposure keratitis from lagophthalmos, inadequate blink, and poor Bell's phenomenon is a significant complication of any blepharoptosis surgery, and particularly so in oculomotor nerve palsy. In a longitudinal series of 316 eyebrow suspensions, Crawford[27] reported an incidence of seven cases of exposure keratitis. In our series, the relatively high rate (30%) of corneal complications in blepharoptosis surgery of oculomotor nerve palsy reconfirms the dangers, stressed by previous authors,[1,2,4] inherent in this surgery. However, the corneal complications were not severe. There were no visually compromising scars. The chronic use of ocular lubricants is common in the treatment of many ophthalmic disorders and is appropriate in the postoperative treatment of these patients.

To minimize corneal complications it is important to reemphasize that appropriate preoperative selection of patients be based on a thorough examination. Essential information includes bilateral fissure size and levator muscle function, extent of hypotropia, vertical ductions, Bell's phenomenon, lagophthalmos, synkinetic movements, corneal sensation, orbicularis muscle function and blink adequacy,

and precorneal tear production and quality.[28] However, the occurrence of exposure keratitis is often not predictable, as stressed by Smith and Bosniak,[29] as demonstrated by the unilateral development of punctate keratopathy after bilateral frontalis sling procedures with equal fissure sizes.

It is prudent to reduce the risks of corneal complications by minimizing postoperative lagophthalmos. Eyebrow suspension procedures and supermaximum levator muscle resections often produce a relatively atonic eyelid and are associated with a greater risk for lagophthalmos for a given postoperative fissure size than are levator muscle aponeurosis advancements with good levator muscle function. Therefore, one should discourage eyelid elevation to purely cosmetic levels in patients with oculomotor nerve palsy who have poor levator muscle function.

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Linear Subcutaneous Fat Atrophy After Corticosteroid Injection of Periocular Hemangiomas

Patrick J. Droste, M.D., Forrest D. Ellis, M.D., Naval Sondhi, M.D., and Eugene M. Helveston, M.D.

Two children developed evidence of subcutaneous fat atrophy after corticosteroid injection of periocular hemangiomas. The atrophy appeared at the site of injection and followed the expected course of lymphatic channels to the vicinity of regional lymph nodes.

THE TREATMENT of capillary hemangiomas with corticosteroid injection has been associated with complications including central retinal artery occlusion,[1] retention of corticosteroid deposits, local fat atrophy,[2] and eyelid necrosis at the site of injection.[3] Blindness has been reported after injection of corticosteroids into the nasal turbinates.[4] Facial injections of corticosteroids have been associated with ischemic crystalline corticosteroid emboli in the retinal circulation.[5] Despite these complications, repository corticosteroids are the current treatment of choice for adnexal hemangiomas.[6]

We recently observed two patients who have developed a linear type of subcutaneous fat atrophy after corticosteroid injection of hemangiomas in the orbital and periorbital regions.

Case Reports

Case 1

A 3½-month-old girl was examined because of a mass in her right lower eyelid and right orbit. Her parents had noted progressive enlargement of the mass, which was either not present or not observed at birth. The parents had noted also that the tumor enlarged and became more blue when the child cried or was held in a head-down position. No changes in size or appearance of the mass specifically associated with upper respiratory infection had been noted.

Examination demonstrated a soft, compressible, blue mass in the right lower eyelid. The mass enlarged when the child cried. The right eye was displaced superiorly within the orbit. A right hypertropia was present. Fixation and following movements were considered to be normal with each eye. Infraduction of the right eye was mildly limited. The right eye was found to be 2 diopters more hyperopic than the left eye. The fundus of each eye was normal.

The tumor had the clinical appearance of a hemangioma, and no other diagnoses were considered likely. Computed tomography demonstrated a right orbital and right lower eyelid mass with the radiologic characteristics of a hemangioma.

The superficial portion of the hemangioma was injected with 1 ml of a 50:50 mixture of triamcinolone acetonide (40 mg/ml) and betamethasone sodium phosphate (6 mg/ml) on two separate occasions, one and two months after the initial examination because of continued growth of the tumor with further displacement of the eye. During the succeeding months, the anterior extension of the hemangioma improved, but the hypertropia, vertical displacement, and proptosis worsened. Approximately eight months later, 2 ml of a 50:50 mixture of triamcinolone diacetate and betamethasone sodium phosphate was injected into the orbital portion of the tumor while an observer viewed the retinal circulation with indirect ophthalmoscopy.

Four months after the orbital injection, a significant reduction in proptosis, strabismus, and vertical displacement had occurred. Two months later, a linear depression appeared inferior to the right lateral canthus and extended laterally to the region of the right preauricular lymph nodes. This area of presumed subcutaneous atrophy remained more or less unchanged for about nine months after the retrobulbar injection, then began to resolve, and

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was not visible 13 months later. Visual acuity has remained equal in each eye but the right hypertropia persists.

Case 2

A 14-month-old girl received three separate corticosteroid injections consisting of a 50:50 mixture of triamcinolone acetonide (40 mg/ml) and betamethasone sodium phosphate (6 mg/ml) over a 12-month period for treatment of a capillary hemangioma of the right upper eyelid and superonasal orbit. When the child was 7 weeks old, 0.5 ml of the above mixture was injected into the right upper eyelid near the site of the lesion (Fig. 1). Another 0.5 ml was injected three weeks later in the same location. A third injection of 1.8 ml was administered when the child was 14 months old (Fig. 2). The total dosage was approximately 3.0 ml.

The treatments were successful in reducing the size of the hemangioma. However, approximately seven months after the last injection, when the girl was 21 months old, a dimple appeared in the right cheek, near the right nasolabial fold. Within three additional months the dimple had evolved into a crease that extended from the right medial canthus and the site of the corticosteroid injections downward to the area of the submandibular lymph nodes (Figs. 3 and 4). Residue from the injections was visible subcutaneously at the injection sites. The crease was prominent in the region where it crossed the mandible. No alteration of the skin was detected. No hemifacial atrophy was present. No erythema or inflammation was associated with the crease. The original lesion had continued to atrophy. Results of the remainder of the ocular and the systemic examination were unremarkable.

Although discussions with the parents included the options of removing the injection

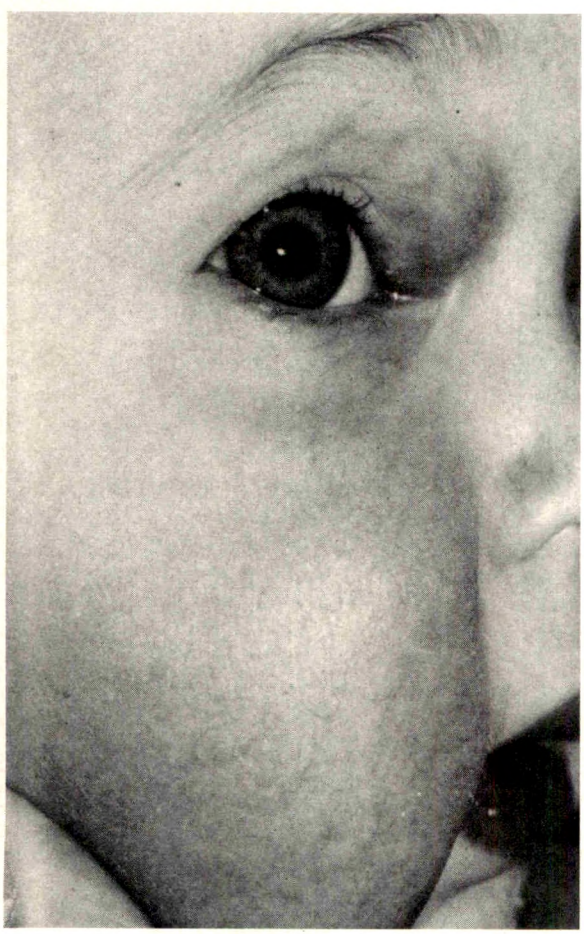


Fig. 1 (Droste and associates). Case 2. Preinjection photograph of a 7-week-old girl with a capillary hemangioma of the right upper eyelid.

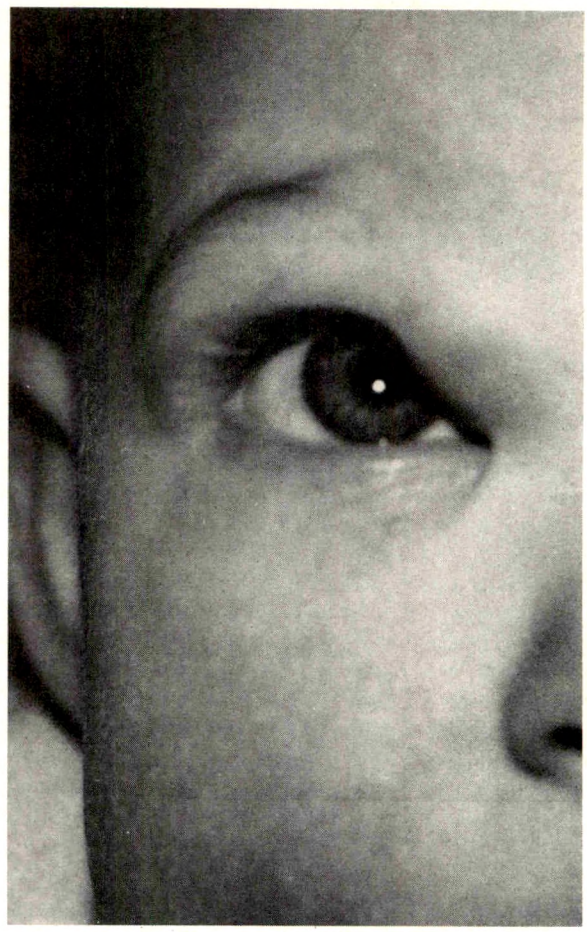


Fig. 2 (Droste and associates). Case 2. Preinjection photograph of same child at 14 months of age. Note absence of any evidence of linear subcutaneous atrophy.

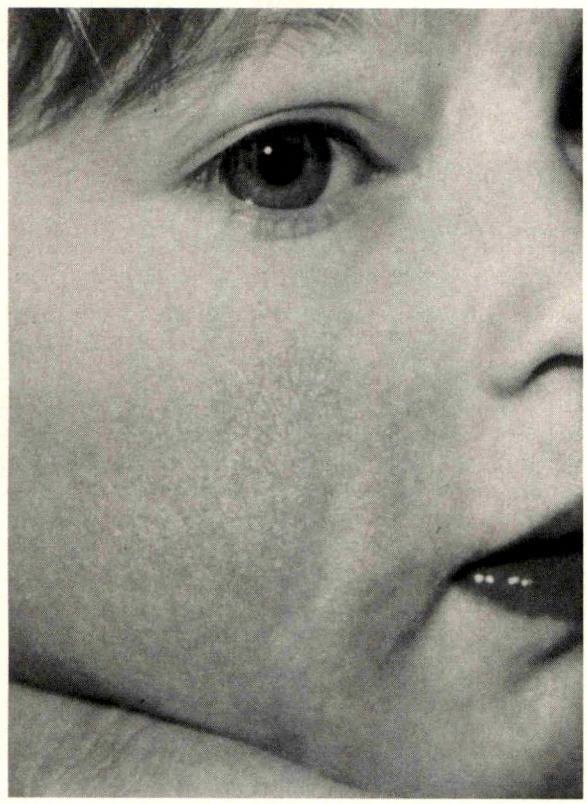


Fig. 3 (Droste and associates). Case 2. Onset of linear subcutaneous atrophy seven months after the last injection of repository corticosteroid. Note the line of atrophy extending from the site of injection in the medial right upper eyelid down across the cheek toward the submandibular area.

residue surgically, no treatment was recommended other than observation. The crease appeared to deepen for about three additional months, then began to diminish in prominence. Eighteen months after the last injection, the crease was just visible and resolution appeared to be continuing.

Discussion

Capillary hemangiomas, the most common ocular adnexal tumors of childhood, are vascular hamartomas that appear in the orbit and the periorbital areas. Usually they appear during the perinatal period, enlarge rapidly over the next few months, remain stable for a period of several months, and involute spontaneously.[7] Resolution, which usually starts in the second year of life, is complete in about 60% of cases by age 4 years and in up to about 76% by age 7 years.[8]

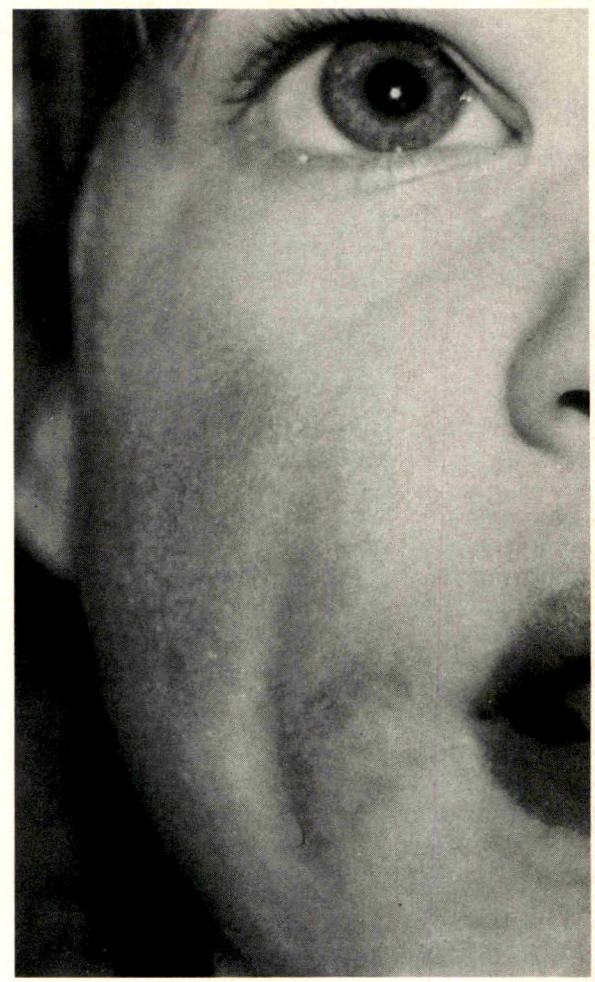


Fig. 4 (Droste and associates). Case 2. Photograph taken at the same time as Figure 3. Note prominent crease over right cheek and mandible.

Children with hemangiomas of the eyelids and orbit are at risk for development of amblyopia, astigmatism, strabismus, proptosis, and compression of the optic nerve. Because of their location, hemangiomas may be unacceptable cosmetically or may produce permanent asymmetry or deformity of adjacent structures.[9]

Many different forms of treatment have been advocated for this condition. They include radiation therapy, cryotherapy, and surgical removal. However, suboptimal results or associated complications have limited the use of these treatment modalities.

Intralesional injection of the hamartomas with corticosteroid preparations, particularly triamcinolone preparations, has become the treatment of choice because of the low incidence of side effects and the generally rapid

reduction of tumor size achieved by this method.[6]

Triamcinolone corticosteroid preparations have been known to produce local fat atrophy.[2,10-14] However, we have been unable to find published reports of a linear type of atrophy developed along local lymphatic channels such as seen in our two cases where the atrophy developed near the site of the injection and extended to the site of regional lymph nodes.

The precise cause of fat atrophy produced by corticosteroid is unknown. Several mechanisms have been postulated. Iuel and Kryger[12] reported a case of persistent subcutaneous fat atrophy two years after the injection of prednisolone tertiary butyl acetate. Biopsy of the affected area disclosed a complete absence of fat cells in the subcutaneous tissue as well as atrophic changes in the cutis. The proposed mechanism was that of a localized lypolysis produced by long-acting corticosteroid crystals deposited in the subcutaneous tissues.[12]

Corticosteroids have been shown to produce or enhance vasoconstriction, especially when administered locally in high concentrations. This enhanced vasoconstriction may facilitate local thrombosis or embolization and capillary closure with resultant local tissue hypoxia. These effects would then produce local tissue atrophy or, in extreme cases, necrosis.[10]

An atypical allergic reaction to repository corticosteroid preparations or their vehicles has also been proposed as a possible mechanism for producing local fat atrophy, presumably through local tissue necrosis.[3,11] This mechanism seems unlikely in our cases since apparent complete recovery has occurred in Case 1 and is nearly complete in Case 2.

We are not certain of the natural course of this condition, but local fat atrophy has been described after corticosteroid injection that, in most cases, resolved within 14 months.[2] Friedman[13] reported nine cases of subcutaneous fat atrophy and skin changes after injection of tributylacetic acid ester of dexamethasone. He observed that the atrophy most frequently developed two months after injection, was associated with thin transparent skin that would not suntan normally, and slowly resolved over a two- or three-month period. He made the observation that the atrophy occurred only in females and that it persisted as long as the corticosteroid crystals remained in the skin.

The age at onset, clinical course, and the absence of erythema or patchy alterations of the skin and subcutaneous tissues in our cases is inconsistent with diagnoses such as linear scleroderma, nonsuppurative panniculitis, or hemifacial atrophy.[15] The possibility of our treating a lymphangioma rather than a hemangioma could be considered since no biopsy of the original tumor was done in either of our cases, but the absence of periodic swelling or of exacerbation with upper respiratory illness and the subsequent clinical courses of our patients make this diagnosis unlikely.

The cases of linear subcutaneous fat atrophy that we have described illustrate an additional complication of corticosteroid infiltration of capillary hemangiomas. Ophthalmologists treating these tumors with corticosteroid preparations should be aware of this potential complication. Parents should be informed that such atrophy might occur. Additional observations must be made before the apparently benign nature of this complication can be confirmed.

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OPHTHALMIC MINIATURE

With great interest, Nicholas took the forked instrument William held out to him. "Oculi de vitro cum capsula!" he cried. "I had heard tell of them from a Brother Jordan I met in Pisa! He said it was less than twenty years since they had been invented. But I spoke with him more than twenty years ago."

"I believe they were invented much earlier," William said, "but they are difficult to make, and require highly expert master glaziers. They cost time and labor. . . ."

Umberto Eco, *The Name of the Rose*
Translated by William Weaver
New York, Harcourt Brace Jovanovich, 1983, p. 86

Postkeratoplasty Crystalline Deposits Mimicking Bacterial Infectious Crystalline Keratopathy

Robert W. Weisenthal, M.D., Jay H. Krachmer, M.D., Robert Folberg, M.D., Steven P. Dunn, M.D., and William E. Whitson, M.D.

Three corneal transplant patients developed white, crystalline, anterior stromal lesions in their grafts while receiving long-term topical corticosteroid therapy. A presumed diagnosis of infectious crystalline keratopathy was made in each case. However, histologic examination of the lesions failed to show gram-positive cocci. A fungal infiltrate was present in the first two patients, and calcium deposits produced the lesion in the third patient.

THE APPEARANCE of slowly progressive, white, refractile, finely branched, anterior stromal infiltrates in patients receiving long-term topical corticosteroid therapy after corneal transplantation, or with recurrent herpes simplex keratitis, suggests the diagnosis of infectious crystalline keratopathy. Infectious crystalline keratopathy is caused by gram-positive cocci, usually *Streptococcus viridans*, which in corneal grafts is difficult to treat. The organism responds poorly to antibiotic therapy, and even if antibiotics are efficacious, significant scarring and vascularization of the graft can result in poor vision. Regrafting is usually necessary to eradicate the infectious process.

We examined three patients with refractile, anterior stromal infiltrates that had been clinically diagnosed as infectious crystalline keratopathy. No patient showed evidence of gram-positive cocci. In two cases a fungal infection was demonstrated, and in the third case, focal stromal calcification was present.

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Case Reports

Case 1

An 85-year-old woman was referred to the Iowa Lions Cornea Center at the University of Iowa for treatment of aphakic bullous keratopathy in the left eye. The patient had undergone intracapsular cataract extractions in 1974 in the right eye and in 1975 in the left eye, as well as a trabeculectomy in 1953 in the left eye. On June 9, 1986, a penetrating keratoplasty with anterior vitrectomy was performed in the left eye. Postoperatively, the patient was given prednisolone sodium phosphate 1% four times a day and timolol maleate 0.5% twice daily. She also received a two-week regimen of topical antibiotics. Methazolamide 50 mg twice daily was also required for intraocular pressure control.

On Sept. 4, 1986, three months after penetrating keratoplasty, while still receiving prednisolone sodium phosphate twice a day, a 0.8 × 1.0-mm, white anterior stromal crystalline opacity appeared in the corneal graft beneath intact epithelium (Fig. 1). A presumed diagnosis of infectious crystalline keratopathy was made, and an excisional biopsy was performed using a 1.5-mm corneal trephine. The entire specimen was fixed in neutral buffered formalin for histologic study. Clinically, the infectious infiltrate was entirely removed. Because the infection was thought to be eradicated, and to provide prophylaxis against graft rejection early in the postkeratoplasty period, an antibiotic-corticosteroid ointment was prescribed. Histopathologic examination of the biopsy specimen disclosed a beaded, branching, filamentous fungus suggestive of *Alternaria* (Fig. 2). No bacteria were demonstrated.

On Sept. 18, 1986, a new fine branching white stromal opacity similar to the initial infiltrate was detected at the base of the corneal biopsy site. Corticosteroid therapy was discontinued, and the patient was given topical 0.1%

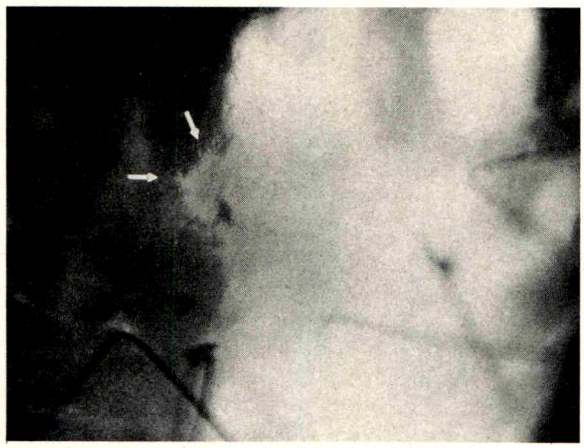


Fig. 1 (Weisenthal and associates). Case 1. Slit-lamp photograph of white anterior stromal crystalline infiltrate in the corneal graft beneath an intact epithelium. Note the needle-like projections of the infiltrate (arrows). There was no surrounding inflammation.

amphotericin B every hour while awake, and every two hours at night. Because the infiltrate enlarged, the lesion was scraped and cultured for bacteria and fungi. Treatment was changed to topical 5% natamycin every two hours. The cultures grew one colony of *Staphylococcus epidermidis*, which was probably a contaminant. The infiltrate slowly decreased, responding well to natamycin therapy. Eventually a small scar formed in the area of previous involvement. The patient has had no further recurrences and has a clear graft. Visual acuity at last examination was counting fingers secondary to optic nerve damage from glaucoma.

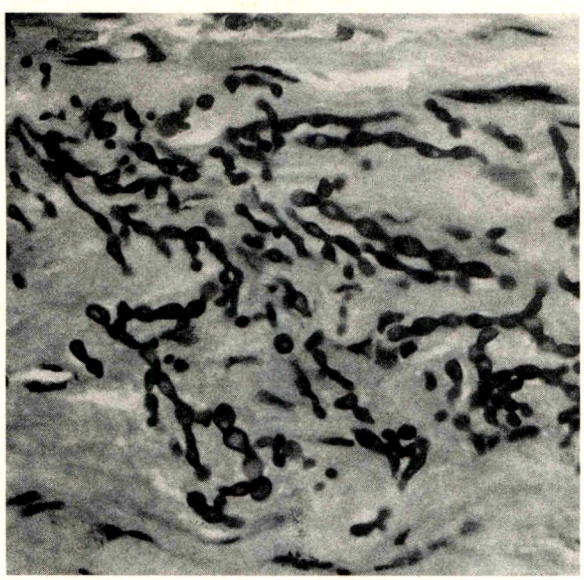


Fig. 2 (Weisenthal and associates). Case 1. Photomicrograph of the biopsy specimen shows a beaded, branching, filamentous fungus, consistent with *Alternaria*. No bacteria were demonstrated (periodic acid-Schiff, ×100).

Case 2

A 75-year-old woman was first examined by one of us (S.P.D.) in September 1985, with pseudophakic bullous keratopathy in her left eye. An uncomplicated penetrating keratoplasty was performed on Oct. 25, 1985. Postoperatively she was treated with topical gentamicin sulfate 3 mg/ml, atropine sulfate 1%, and prednisolone acetate 1%. Her postoperative course was uneventful until late November 1985, at which time a single, small, branching anterior and midstromal lesion appeared beneath intact epithelium at the 7 o'clock meridian in the graft. The infiltrate was refractile in retroillumination. No surrounding inflammation was noted. Bacterial and fungal cultures were negative. A presumed diagnosis of infectious crystalline keratopathy was made and the patient was given hourly topical cefazolin 50 mg/ml; the topical corticosteroid was discontinued. The infiltration became smaller and scarred. Topical antibiotics were gradually tapered over the next four months.

In April 1986 the patient was found to have multiple keratic precipitates. Prednisolone acetate 1% was begun four times a day to treat a presumed mild graft rejection. The topical corticosteroid was tapered over a month. On May 7, 1986, the patient complained of irritation in the left eye. Examination disclosed two areas of mid to deep stromal infiltration at the site of the original infection (Fig. 3). There was a mild anterior chamber reaction. A presumed diagnosis of recurrent infectious bacterial crystalline keratopathy was made. However, corneal cultures and the biopsy specimen grew *Candida tropicalis*. A regimen of topical amphotericin B 0.15% every hour was begun.

Two weeks later a small vitreous opacity was observed and oral ketoconazole 200 mg was administered every four hours. A diagnostic and therapeutic vitrectomy with intraoperative injection of amphotericin B was performed on May 29, 1986. Intraoperative cultures grew *C. tropicalis*, which was sensitive to amphotericin B, ketoconazole, miconazole, and flucytosine. Oral ketoconazole was used until the patient developed increased levels of hepatic enzymes. Topical amphotericin B was then given for four months. The infiltrate slowly decreased in size and scarred with treatment.

The patient was again found to have subepi-

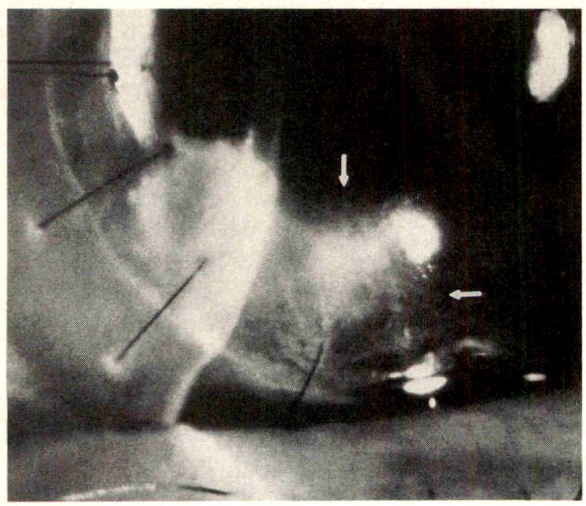


Fig. 3 (Weisenthal and associates). Case 2. Slit-lamp photograph of two areas of refractile stromal opacities associated with discrete, fine, fern-like projections (arrows).

thelial infiltrates and scattered keratic precipitates in November 1986. Prednisolone acetate solution was begun every hour along with dexamethasone 0.1% ointment at night. The rejection reaction responded to topical therapy. However, the corneal infiltrate increased in size, necessitating a repeat corneal transplant on Dec. 22, 1986. Cultures and pathologic sections confirmed the presence of *Candida* (Fig. 4). Her postoperative course has been uneventful, with no evidence of recurrence. At the last

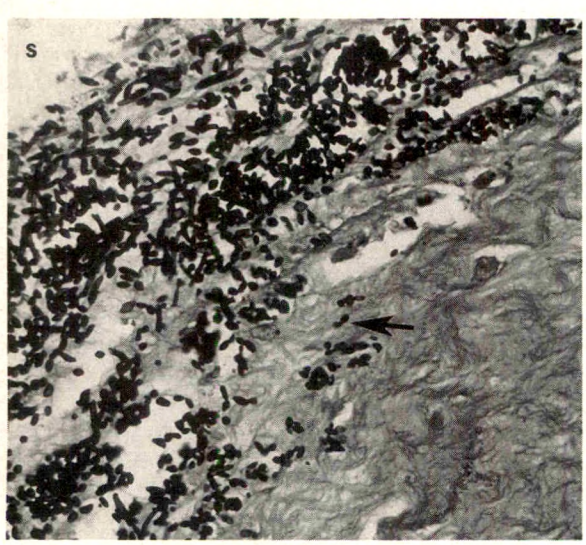


Fig. 4 (Weisenthal and associates). Case 2. The superficial stroma is infiltrated by *Candida* organisms. S, corneal surface; arrow, pseudohypha (periodic acid-Schiff, ×50).

examination best corrected visual acuity was 20/100 secondary to cystoid macular edema.

Case 3

A 58-year-old man was examined at the Iowa Lions Cornea Center on Dec. 14, 1985, with a severe herpes simplex keratouveitis in the left eye. Visual acuity was R.E.: 20/20 and L.E.: hand motions. No afferent pupillary defect was present. Corneal sensation was absent in the left eye. On slit-lamp examination the right eye was normal. In the left eye there was a central 2 × 2-mm geographic epithelial defect, with underlying stromal edema and folds in Descemet's membrane. There was 2+ cell and flare in the anterior chamber. Intraocular pressure was R.E.: 19 mm Hg and L.E.: 50 mm Hg. The patient was given prednisolone sodium phosphate 1% and trifluridine four times a day, as well as timolol maleate 0.5% and acetazolamide 500 mg twice daily. The patient was subsequently lost to follow-up.

On Feb. 10, 1986, the patient returned to the clinic with a central corneal perforation. The perforation was initially treated with tissue adhesive and a bandage soft contact lens. However, the area of perforation continued to leak and on March 14, 1986, an 8.0-mm penetrating keratoplasty was performed. Postoperatively the graft did not reepithelialize, despite a prolonged regimen of patching followed by a bandage soft contact lens. On June 16, 1986, a partial tarsorrhaphy was performed. The patient was given neomycin sulfate-dexamethasone sodium phosphate ointment, and timolol maleate 0.5% and trifluridine solution twice daily. The epithelium healed slowly over the next several months, and the inflammation subsided.

On Nov. 19, 1986, while still using neomycin sulfate-dexamethasone sodium phosphate ointment, the patient complained of a red itchy eye; the tarsorrhaphy was opened. The corneal graft was hazy with epithelial and stromal edema. The sutures were loose and an epithelial defect was present inferonasally associated with a wound leak. A crystalline-appearing stromal opacity measuring 1 × 1 mm was seen superficially in the superonasal quadrant of the graft (Fig. 5). There were fine branching peripheral finger-like projections. The anterior chamber was shallow but quiet, and a dense cataract was present. The diagnosis of graft failure with wound leak was made. Because of the clinical appearance of the crystalline infiltrate, a presumed diagnosis of infectious crystalline keratopathy was also made. A second

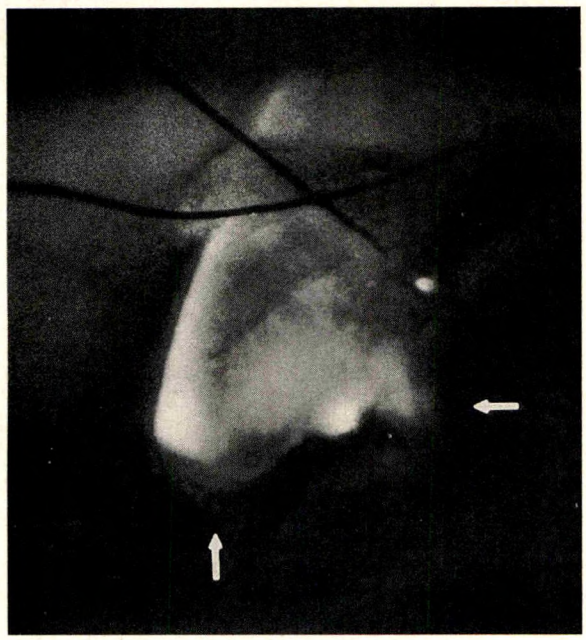


Fig. 5 (Weisenthal and associates). Case 3. Slit-lamp photograph of anterior stromal crystalline opacity in the superonasal portion of the corneal graft. Note the peripheral finger-like projections (arrows) and the lack of surrounding inflammation.

penetrating keratoplasty with extracapsular cataract extraction was performed to remove the failed graft and excise the crystalline infiltrate.

Histopathologic examination of the graft disclosed calcium deposits in the area of the crystalline opacities, with no evidence of bacteria or fungi (Fig. 6). Cultures of the graft were negative. Postoperatively erosions and ulcers recalcitrant to medical therapy developed. A conjunctival flap was performed, which limited visual acuity to counting fingers at our last examination.

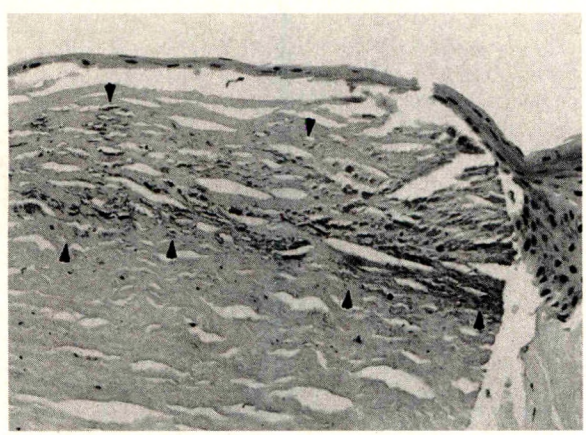


Fig. 6 (Weisenthal and associates). Case 3. Basophilic calcium deposits (arrowheads) seen in the corneal specimen excised at the time of surgery. No bacteria or fungi were noted. The incision is the site of the graft-host interface (hematoxylin and eosin, ×16).

Discussion

Infectious crystalline keratopathy, a term coined by Meisler and associates,[1] is characterized by a slowly progressive, superficial infiltrate found in patients receiving long-term corticosteroid therapy. Gorovoy and associates[2] initially described the keratopathy as a noninflammatory colonization of bacteria, because there were no signs of ocular inflammation in the presence of a bacterial infection. They speculated that long-term corticosteroid therapy inhibited inflammatory response to this infection. This is supported by a recent case report by Samples, Baumgartner, and Binder,[3] in which a suppurative process developed upon cessation of corticosteroid therapy.

In a review of the literature, Reiss, Campbell, and Bourne[4] compiled eight cases of infectious crystalline keratopathy based on clinical diagnosis. Seven patients had previous corneal transplants, two of which were for the treatment of herpes simplex keratitis. One patient had recurrent herpes simplex keratouveitis without a history of surgery. In four of eight cases, *S. viridans* was cultured from a biopsy specimen of the infiltrate. In seven patients the trilamellar cell wall characteristic of a coccal bacteria was demonstrated on transmission electron microscopy. Recently, two additional cases of midstromal, crystalline, bacterial infiltrates in corneal grafts have been reported.[5,6] In both cases cultures were negative, but gram-positive cocci were demonstrated on histologic examination. Thus, it appears that histologic examination is more sensitive than culture for diagnosis.

Streptococcus viridans has been identified as the cause of the infiltrate in almost all previously reported cases. It is a fastidious organism that grows slowly in culture, and is not usually virulent. Recently, anaerobic peptostreptococcus[7] and *Haemophilus aphrophilus*[8] have also been reported to cause an anterior stromal or midstromal filamentous keratitis clinically similar to infectious crystalline keratopathy.

Therapy for infectious crystalline keratopathy from bacterial infection requires discontinuation of topical corticosteroids and fre-

quent application of fortified broad-spectrum antibiotics. However, as emphasized by Kincaid and Snip,[5] the infection is usually progressive despite intensive antibiotic therapy. In ten previously reported cases of infectious crystalline keratopathy, at least five patients required repeat corneal grafts to eradicate the infection.[1-6,9] In the other cases extensive scarring and vascularization developed in the areas of involvement, producing opacified or edematous grafts with poor vision (D. M. Meisler, M.D., oral communication).

Herein, we described three patients with white, refractile, superficial and midstromal infiltrates that were initially incorrectly diagnosed as infectious bacterial crystalline keratopathy. All patients had corneal transplants, were receiving long-term topical corticosteroid therapy, and had a clinical picture similar to those cases described previously.[1-6,9] Because the medical history and clinical findings were consistent with infectious crystalline keratopathy, we did not consider any other infectious agents. However, rather than being secondary to *S. viridans*, the infiltrate was caused by fungus in two patients and calcium deposits in the third patient. Although fungal infections can appear as fine, filamentous stromal infiltrates, in our two patients the lesions also had a crystalline appearance. This prompted us to diagnose infectious crystalline keratopathy, and not suspect an underlying fungal infection.

In the first patient a small excisional biopsy and aggressive antifungal therapy were sufficient to resolve the fungal infection without need for further surgery. In the second patient the fungal infiltrate was partially treated, and then progressed when topical corticosteroids were required to treat a rejection reaction. In the third patient the calcium deposits were innocuous.

In cases of crystalline deposits in corneal transplants, we recommend an excisional biopsy and microbiologic and histologic studies be performed to rule out possible causes other than infectious crystalline keratopathy. Histologic examination is more sensitive than culture in identifying both *S. viridans* and fungal organisms, especially in partially treated infections. Although infection secondary to *S. viridans* is difficult to treat and often requires penetrating keratoplasty, there are other more benign causes of this same clinical picture that offer a better prognosis with appropriate treatment.

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Bilateral Keratitis as a Manifestation of Lyme Disease

Jules Baum, M.D., Michael Barza, M.D., Philip Weinstein, M.D., Joseph Groden, M.D., and Milhim Aswad, M.D.

An 11-year-old girl developed bilateral keratitis, which we believe was a manifestation of Lyme disease. She had had several attacks of Lyme arthritis and was twice treated with parenteral penicillin. The keratitis developed five years after the initial episode of Lyme arthritis at a time when there were no other manifestations of Lyme disease. It cleared completely in both eyes after topical corticosteroid therapy.

Conjunctivitis is the most commonly reported ocular complication of Lyme disease,[1-4] with an incidence of 11% (35 of 314 cases) in one series.[2] A few patients have experienced temporarily blurred vision that was attributed to an increase in intracranial pressure,[5] while others have had photophobia[2] or diplopia associated with either oculomotor or abducens nerve paresis.[6,7] There are single case reports of ischemic optic neuropathy[8] and iritis followed by panophthalmitis.[4] In one experimental study, *Borrelia burgdorferi* was recovered from the eyes in nine of 20 hamsters after intraperitoneal injection of the organism, but details of the ocular findings were not given.[4] We describe here a girl who developed bilateral keratitis as a result of Lyme disease.

Case Report

An 11-year-old girl, living in Connecticut, first became ill in May 1981 after a tick bite. She developed pain in her hands and knees and a clinical diagnosis of Lyme arthritis was made. The symptoms gradually resolved on treatment with aspirin. In March 1983 she developed an effusion in her left knee. Her erythrocyte sedimentation rate was normal and tests for cryoglobulins, rheumatoid factor, and antinuclear antibody were negative. The symptoms again resolved on treatment with aspirin. The knee effusion recurred in April 1984. Serologic tests for *B. burgdorferi* using immunofluorescent antibody were positive on April 17, 1984, at a titer of 1:512; on May 1, 1984, the titer was >1:2,048. The patient was treated with three weekly intramuscular injections of 600,000 units of benzathine penicillin G. Her symptoms improved markedly and she resumed full activity until March 1986. At that time she developed pain with some swelling in the left wrist. Results of complete blood cell count, erythrocyte sedimentation rate, rheumatoid factor, and antinuclear antibody tests were again normal or negative and a repeat serologic test for *B. burgdorferi* was positive at a titer of 1:2,048. Her symptoms improved on treatment with aspirin. She was hospitalized and treated with 12 million units of penicillin G daily for three weeks.

She did well until September 1986, when she noted the onset of decreased vision in the right eye and occasional photophobia without redness or tearing. The symptoms persisted for two months. Two years previously she had noted similar photophobia, which resolved spontaneously after four months. On Oct. 30, 1986, her best corrected visual acuity was R.E.: 20/70 and L.E.: 20/40. The conjunctivae were normal.

Minimal punctate staining of the corneal epithelium was seen in the right but not the left eye. The right cornea demonstrated multiple focal hazy stromal opacities involving the visual axis and reaching the temporal but not the nasal corneoscleral limbus (Figure). These opacities overlapped and had indistinct borders. They were seen at two different levels. Some were restricted to the area of the epithelial basement membrane, while others involved

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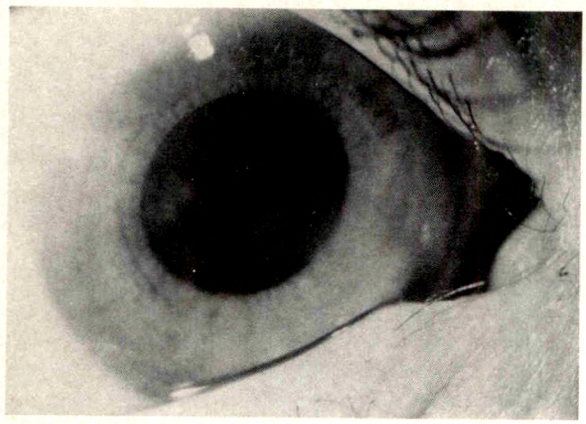


Figure (Baum and associates). Right eye. Note multiple focal hazy corneal stromal opacities with indistinct borders.

both superficial and deep stroma. The left cornea had opacities that involved only the inferonasal quadrant. Some of the opacities involved the entire stromal thickness, while others had a pattern similar to that seen in the right cornea. Stromal edema was noted in the right but not the left cornea. A single anterior stromal blood vessel was seen in each cornea extending 2 mm into the stroma. The endothelium in each eye was irregular but without keratic precipitates or cornea guttate lesions. The anterior chambers and the pupil were normal and the rest of the ocular examination was unremarkable.

Prednisolone acetate 1% eyedrops four times daily were started in the right eye. The infiltrates diminished and visual acuity improved to 20/40+3 with faint deep corneal opacities persisting. Visual acuity in the left eye remained stable at 20/40, but the opacities became more dense. Prednisolone acetate 1% eyedrops four times daily were started in the left eye; they were continued in the right eye but at a dosage interval of once daily.

Over the next two months the frequency of the applications of the eyedrops was tapered and then discontinued in each eye as the opacities decreased and then resolved. A moderate recurrence of the stromal infiltrates occurred in the right eye one month after discontinuing topical corticosteroid treatment. Reinstitution of similar therapy cleared the cornea in approximately one month, at which time the treatment was discontinued with no sign of recurrence. Both corneas have remained clear without treatment for the past several months and visual acuity is now 20/25 in each eye. Serologic titers against *B. burgdorferi* in June (before hospitalization), September, and December 1986 were 12.1, 12.3, and 11.8 for IgG-enzyme immunoassay capture assay (optical density ratio) and 3.1, 2.7, and 2.8 for IgM-enzyme immunoassay capture assay (optical density ratio). Compared to normal values of <2.5 for IgG and <1.5 for IgM, these are increased and in the range found in chronic Lyme disease.

The fluorescent treponemal antibody absorption test for syphilis in June and September 1986 showed 2+ activity, but the rapid plasma reagin tests were negative. Both parents demonstrated negative results on both tests. Immunoblot testing with *B. burgdorferi* antigen confirmed an infection with that agent and the pattern was typical of that seen in chronic Lyme disease (Victor Berardi, written communication, Feb. 23, 1987). There were no detectable IgG antibodies to the capsid antigen of Epstein-Barr virus in blood samples taken in June and September 1986.

Discussion

Our patient's keratitis was probably a complication of her Lyme disease because no other cause was found, because she was known to have Lyme disease, and because a related spirochete, *Treponema pallidum*, is recognized to produce bilateral diffuse stromal keratitis, albeit of a more fulminant nature. Acute syphilitic keratitis, although rare today, is invariably accompanied by early and massive neovascularization of the cornea. This was not the case in our patient. Although the fluoresecent treponemal antibody absorption test for syphilis was of borderline reactivity in our patient, cross-reactivity may occur in patients with chronic Lyme disease.[9] The results of the rapid plasma reagin and immunoblot tests, together with the epidemiologic history, make syphilitic infection unlikely in this patient. The clinical findings in our patient of a bilateral, patchy keratitis involving both superficial and deep stroma is clinically distinguishable from that reported in syphilitic keratitis.

Other diseases such as infectious mononucleosis, mumps, padi keratitis, and Dimmer's nummular keratitis may also produce a somewhat similar interstitial keratitis,[10] but there is no other evidence to support any of those

considerations in our patient. The stromal infiltration in each eye was worsening before treatment. Whether corneal neovascularization would have commenced if corticosteroid therapy had not been instituted or whether untreated syphilitic and the putative Lyme disease keratitis would resemble each other more closely with the passage of time is conjectural. We were not able to obtain material for direct histologic examination or culture, so our diagnosis remains inferential. We were also not able to distinguish whether the corneal lesions were the direct result of infection by *B. burgdorferi* or might have been the result of an antigen-antibody reaction or some other immunologic phenomenon in the cornea. However, an immunologic reaction of some kind seems more likely than simple infection, and this is the presumption on which our ocular treatment was based. Since episodic recurrences of clinical activity in syphilis are believed to be related to persistence of the antigen, either in living sequestered organisms or fragments of organisms in treated patients, the same kind of events may also occur with Lyme disease. This unusual form of keratitis, if its origin is substantiated by future cases, may prove suggestive of Lyme disease. This feature is all the more important because the keratitis occurred at a time when other systemic manifestations of Lyme disease were in remission.

Acknowledgment

Victor Berardi, Massachusetts Department of Health, Boston, Massachusetts, performed and interpreted the serologic tests done in 1986.

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Ophthalmic miniature

But his eyes, too close together, were not so nobly set in his head as those of the king of beasts are in his, and they were sharp rather than bright-pointed weapons with little surface to betray them. They had no depth or change; they glittered, and they opened and shut. So far, and waiving their use to himself, a clock maker could have made a better pair.

F. G. de Fontaine, *The Fireside Dickens*
New York, Dillingham, 1888

Decreased Expression of HLA Class II Antigens on Human Uveal Melanoma Cells After In Vivo X-ray Irradiation

Martine J. Jager, M.D., Jeroen P. van der Pol, M.D., Didi de Wolff-Rouendaal, M.D., Paul T. V. M. de Jong, M.D., and Dirk J. Ruiter, M.D.

In order to determine the presence of HLA antigens on human uveal melanomas, we tested anti-HLA monoclonal antibodies on tissue sections of these tumors. A great variety in expression of HLA class I and II antigens was present. A significantly lower expression of HLA class II antigens was present on uveal melanomas that had been irradiated before enucleation. These tumors lacked a lymphocytic infiltrate in comparison with non-irradiated tumors. These data suggest that radiotherapy affects expression of histocompatibility antigens on tumors.

SEVERAL FACTORS exert an influence on prognosis in patients with uveal melanoma, for example, tumor cell type, localization, size, and depth of scleral invasion.[1-3] Differences in the clinicobiological behavior between tumors as observed after enucleation may be influenced by the time interval between the development of the tumor and the time of removal, while recognition of the tumor by the immune system may play a role as well.[4,5] HLA antigens are glycoproteins that are essential for antigen recognition by the immune system. The quantity of HLA class I and II antigens on tumor cells may influence the level of immune reactions.[6] Uveal melanomas show heterogeneity in the level of expression of tumor-associated antigens,[7] but it is not yet known whether such differences are present in HLA antigen expression.

HLA class I antigens are expressed on almost all nucleated cells and function as a target to cytotoxic T cells. In the eye, these antigens have been demonstrated on the anterior border of the iris, the epithelium and external basement membrane of the ciliary body, and on the endothelial cells of the choroidal vessels.[8] Oncogenicity of certain viruses to rodent cells[9] was shown to depend on their capacity to decrease class I expression of infected cells, resulting in less recognition of class I negative transfected cells by T lymphocytes. Expression of class I antigens may also be essential for the elimination of virally infected cells and malignant cells in humans.

HLA class II antigens are mainly expressed on cells involved in the immune response and regulate communication between these cells and presentation of antigen to helper T cells.[10] At least three different class II products have been identified, subsequently called DR, DQ, and DP, but no clear functional differences between these products have as yet been found. Class II antigens have been demonstrated on scattered cells throughout the entire uvea.[8]

Although data concerning HLA expression of uveal melanomas are lacking, data on HLA and skin melanomas are abundant. Human cutaneous melanomas show heterogeneous expression of both class I and class II antigens, with changes in expression during the course of tumor progression: HLA class I antigens are found on few common nevocellular nevi, but in most primary cutaneous melanomas.[11] Class II expression is not observed in nevi, but is common in cutaneous melanomas, and is associated with increased tumor thickness and early metastasis.[12,13] Class I and II antigen expression is more pronounced in the presence of a lymphocytic infiltrate.[11]

We know many prognostic factors in uveal

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melanomas with regard to life expectancy[1-3] but still are unaware of the underlying mechanisms. Immunologic factors like expression (or lack of expression) of HLA antigens may play a major role in recognition of a tumor or of early metastases.

The purpose of this study was to determine whether variable levels of expression of HLA class I and II antigens exist in human uveal melanomas. A panel of different anti-HLA monoclonal antibodies was applied to tumor specimens. HLA expression was compared to clinicopathologic characteristics of these tumors, such as tumor size, cell type, and scleral invasion, as well as to age and sex of the patient.

Material and Methods

Specimens were obtained from 27 uveal melanomas after enucleation (Table 1). Immediately after enucleation a portion of each tumor was transsclerally removed under transillumination and snap-frozen in OCT compound and stored at −70 C. The remainder of each specimen was processed for histopathologic examination.

Tumors were obtained from three locations (Universities of Amsterdam, Leiden, and Rotterdam). Nine melanomas were obtained from a location (Rotterdam) where, in the context of another investigation, eyes were irradiated on the last two days before enucleation with 4-Gy electron beam irradiation, totaling 8 Gy.

Histopathologic examination—In each case, the diagnosis was established by using conventional histologic sections stained with hematoxylin and eosin prepared from paraffin-embedded tissue, and celloidin-embedded tissue. Cell type (spindle, mixed, or epithelioid), pigmentation (absent, less than half of the cells, more than half of the cells pigmented, or heavily pigmented), mitotic frequency, lymphocytic infiltration, necrosis, tumor diameter, tumor elevation, vasoinvasive growth, and scleral invasion (absent, slight, moderate, deep, or episcleral) were determined in all of these preparations by one of us (D.W.-R.). The presence and intensity of inflammatory infiltrate (absent, scarce, or present) was assessed on 4-μm-thick toluidine blue-stained frozen sections taken immediately adjacent to the sections to be used in the immunoperoxidase procedure.

Immunoperoxidase study—Frozen sections 4 μm thick were air-dried and fixed in acetone for ten minutes. Sections were incubated for 60 minutes at room temperature with a monoclonal antibody diluted in phosphate-buffered saline and then for 30 minutes with rabbit anti-mouse immunoglobulin-horseradish peroxidase conjugate. Between the two incubations, sections were washed three times with phosphate-buffered saline (pH 7.4). Staining was achieved by incubation of sections in an acetate buffer solution (pH 5.0) that contained 3-amino-9-ethylcarbazole, dimethylformamide, and hydrogen peroxide. Finally, the sections were washed in acetate buffer, counterstained in Mayer's hematoxylin, and coverslipped with Aquamount (Gurr, BDH Chemicals Ltd.). As a

TABLE 1
CLINICAL AND HISTOPATHOLOGIC DATA OF 27 UVEAL MELANOMAS

PATIENT SEX, AGE (YRS)	EYE	TUMOR NO.	CELL TYPE	DIAMETER (MM)	PROMINENCE (MM)	SCLERAL INVASION
F, 49	RE	1*	Mixed	15.0	9.0	Absent
F, 62	LE	2*	Mixed	11.0	2.5	Absent
F, 36	RE	3†	Spindle	11.0	11.0	Deep
M, 35	LE	4†	Mixed	16.0	1.5	Deep
F, 37	LE	5†	Epithelioid	—‡	—‡	Absent
F, 73	LE	6†	Spindle	11.0	2.5	Slight
F, 59	LE	7†	Epithelioid	15.0	5.0	Episcleral
M, 50	LE	8†	Mixed	15.0	7.0	Episcleral
M, 53	RE	9†	Mixed	10.0	4.0	Slight
M, 64	RE	10	Mixed	16.0	9.0	Slight
F, 40	RE	11	Spindle	15.0	5.0	Deep
F, 80	LE	12	Mixed	13.0	3.0	Slight
M, 63	RE	13	Spindle	12.0	7.0	Deep
F, 57	RE	14	Mixed	11.5	5.5	Moderate
M, 63	RE	15	Spindle	14.0	9.0	Slight
F, 58	LE	16	Epithelioid	12.0	9.0	Episcleral
F, 52	LE	17	Epithelioid	22.0	9.0	Moderate
M, 67	LE	18	Spindle	15.0	8.0	—‡
M, 21	RE	19	Spindle	12.0	3.5	Moderate
M, 78	RE	20	Spindle	15.0	9.0	Episcleral
F, 30	LE	21	Mixed	13.0	9.0	Moderate
M, 49	LE	22	Mixed	16.0	12.0	Deep
M, 66	RE	23	Epithelioid	17.0	12.0	Moderate
F, 62	RE	24	Mixed	16.0	6.0	Episcleral
M, 54	RE	25	Epithelioid	12.0	4.0	Deep
M, 70	LE	26	Spindle	9.0	2.0	Slight
M, 61	RE	27	Mixed	14.0	14.0	Episcleral

*Used in first study only.
†Used in both studies.
‡Could not be determined because of preparational artifacts.

control, a section was not incubated with a monoclonal antibody but with saline. Lack of standardization of monoclonal antibodies for both affinity and avidity may lead to differences in reactivity. In order to minimize such variability, monoclonal antibodies were always first calibrated against sections of skin melanomas with known reaction patterns.[12]

The percentage of positively staining tumor cells was assessed by light microscopy by three independent investigators as previously reported in cutaneous melanomas.[11] The results of the three investigators deviated maximally 10%, and average scores were used in the calculations. Positive reactions were identified by a red color, making differentiation from brown-black melanin pigment possible.

Monoclonal antibodies—Initially we tested nine tumors with three monoclonal antibodies against HLA class I, one against β_2-microglobulin (a molecule associated with class I antigens), and six against the HLA class II antigens. Because of lack of tumor tissue, the second part of the study comprised only seven of these nine tumors, as well as 18 new ones (Table 2). One monoclonal antibody of each specificity with clear positive reactions against the tumors was used for testing against 25 melanomas.[14-20]

Statistical analysis—The Spearman rank correlation test for two quantitative variables, calculating two-sided P values, or the K-samples test was applied.

TABLE 2
MONOCLONAL ANTIBODIES USED IN THIS STUDY AND NUMBER OF TUMORS TESTED

SPECIFICITY	MONOCLONAL ANTIBODY	NO. IN FIRST STUDY	NO. IN SECOND STUDY	
			NON-IRRADIATED	IRRADIATED
HLA class I	W6/32	9	16	6
	BRL	9	16	6
	B1.23.22	9	0	0
β_2-microglobulin	—	9	16	7
HLA class II				
DR	B8.11.2	9	0	0
DR	SV2841	9	0	0
DR-β	SV1254	9	16	9
DP	FA	8	16	9
DQ	Leu 10	9	0	0
DQ	L3.8	9	16	9

Results

In all tumors, positive staining occurred with different numbers of tumor cells, macrophages, or endothelial cells. The percentage of tumor cells staining positively was determined in areas that were clearly recognizable as consisting of malignant cells.

In the first part of the study different monoclonal antibodies against the same specificities were tested to determine whether they reacted in a similar manner. Two (BRL and B1.23.22) of the three monoclonal antibodies against HLA class I gave identical results, and showed a distinct reaction with five out of the nine tumors; the third one (W6/32) reacted with all tumors (Fig. 1). The monoclonal antibody reacting against β_2-microglobulin showed the same or more reactivity than BRL/B1.23.22 and less reactivity than W6/32.

Monoclonal antibodies directed against HLA class II antigens reacted with less cells than the monoclonal antibodies against HLA class I antigens (Fig. 2). Staining with the three anti-HLA-DR monoclonal antibodies resulted in the same percentages: two tumors were highly DR positive, three tumors had DR antigens on one third of their cells, and the remaining four tumors had DR antigens on less than 20% of their cells. Several tumors showed different levels of expression in different areas. Anti-HLA-DP showed a similar or lower expression than DR. The two anti-HLA-DQ antibodies reacted in the same way, and expression was always lower than of DR or DP. Most tumors had less than 1% DQ positive cells.

To determine the frequency of occurrence of the antigens involved we selected one monoclonal antibody of each category and tested them on a total of 25 uveal melanomas.

Results of the monoclonal antibody tests on 25 tumors in the second part of the study are given in Figure 3. These tumors have also been used to determine the expression of cutaneous melanoma-associated antigens on uveal melanomas, which results are described elsewhere.[21] The tumors in the second part of the study showed the same variation in HLA class I and II expression as those in the first part (Fig. 2). Levels of class I antigens and of β_2-microglobulin were higher than the levels of HLA class II antigens. In general, DQ showed a lower expression than DR and DP.

No correlations were observed between expression of any of the antigens and any tumor

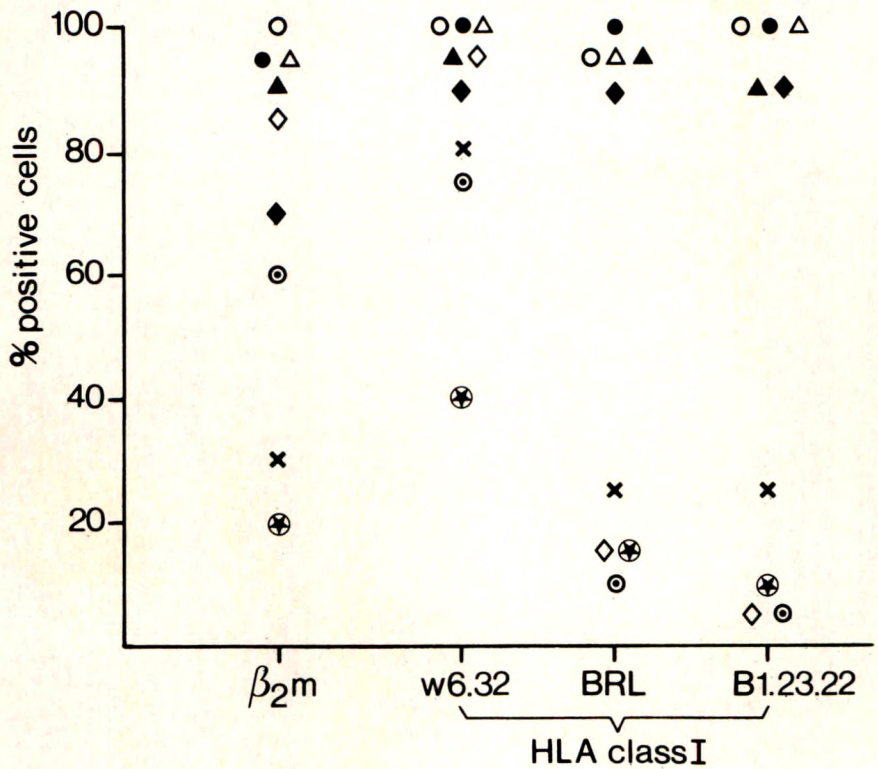


Fig. 1 (Jager and associates). Percentage of positively staining tumor cells in nine tumors. One symbol indicates one tumor. One monoclonal antibody against β_2-microglobulin and three against HLA class I were used.

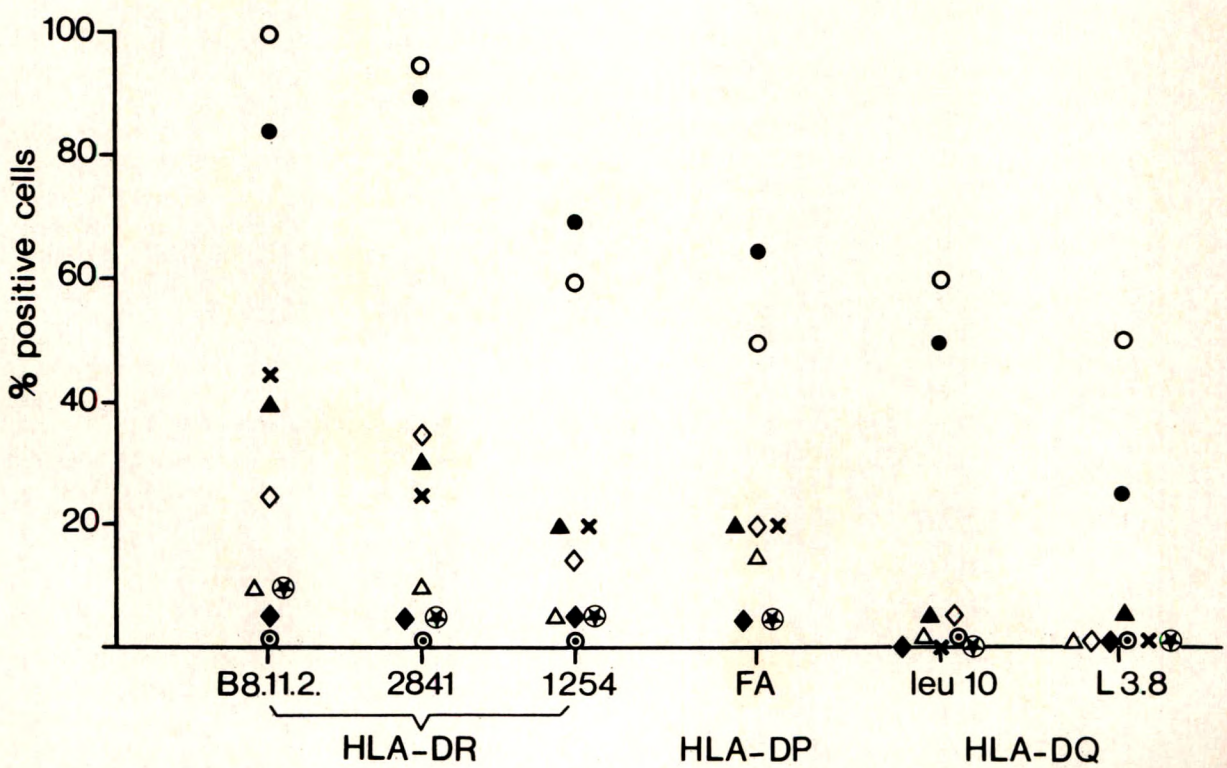


Fig. 2 (Jager and associates). Percentages of tumor cells staining positively for HLA class II antigens -DR (three monoclonals), -DP (one monoclonal), and -DQ (two monoclonals).

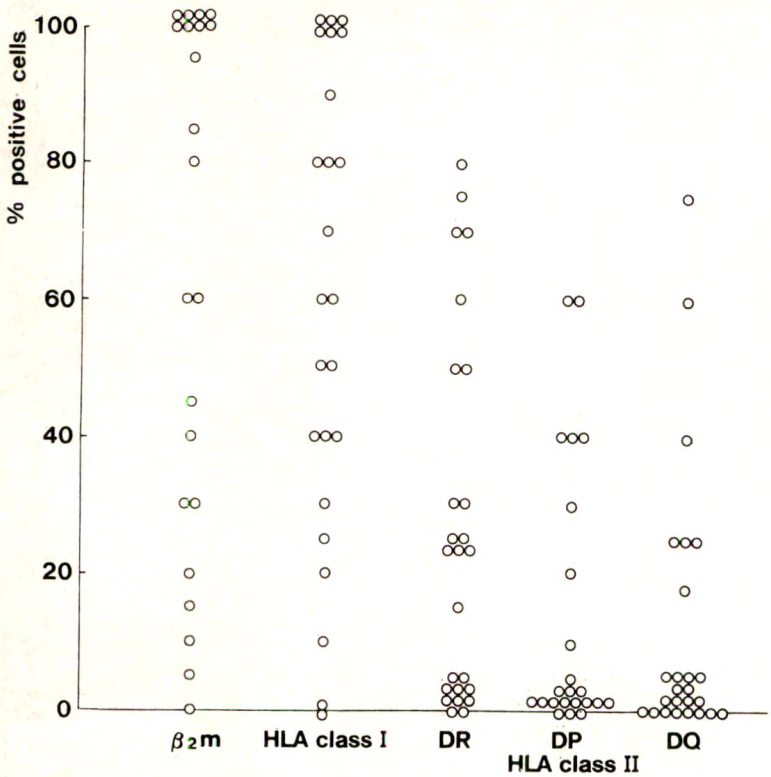


Fig. 3 (Jager and associates). Percentages of positive staining with different monoclonal antibodies in tumor cells of 25 uveal melanomas. One dot represents one tumor. Because of lack of tissue some tumors were not tested with all monoclonal antibodies.

factors, such as diameter, elevation, scleral invasion, tumor cell type, and age and sex of the patient. No correlation was observed between external electron beam irradiation with 8 Gy before enucleation and β^2-microglobulin or class I expression (Fig. 4). A strong correlation, however, was observed between irradiation of the eye on the two days before enucleation, absence of class II antigens, and absence of infiltrate in the tumor. All irradiated tumors but one showed a significantly lower expression of class II HLA antigen in comparison with the nonirradiated ones (Fig. 5, Table 3). The respective P values were as follows: DR, $P = .003$; DP, $P = .021$, and DQ, $P = .006$. There also was a significant difference in lymphocytic infiltrate between irradiated and nonirradiated tumors ($P < .001$).

Discussion

The uveal melanomas tested showed a great variability in expression of HLA class I and II antigens. The reason for this phenomenon is unknown: expression may have been caused by intrinsic factors such as the state of differentiation of the tumor, oncogenes, and cell type, or expression may have been caused by external factors such as the presence of lymphokines, for example, interferon. In cutaneous melanomas a relationship was observed between expression of the HLA antigens and the presence of a lymphocytic infiltrate.[11] In our study HLA class I antigens were expressed on most tumors and the average percentage of expression was higher than of class II. The discrepancy between W6/32 and the other two anti-HLA class I monoclonal antibodies and anti-β_2-microglobulin was obvious but not understood. There was a decreasing expression of DR, DP, and DQ antigens, respectively. Because variations in avidity and affinity between monoclonal antibodies may also cause differences in staining, one has to be careful with the interpretation of such data. However, our monoclonal antibodies with the same specificities showed similar reaction patterns, and the same hierarchy in expression of DR, DP, and DQ has also been reported for leukemic cells[22] and normal class II positive tissues.[23] In our study this sequence was not only observed in nonirradiated but also in the irradiated samples.

In nonirradiated tumors a great variety in

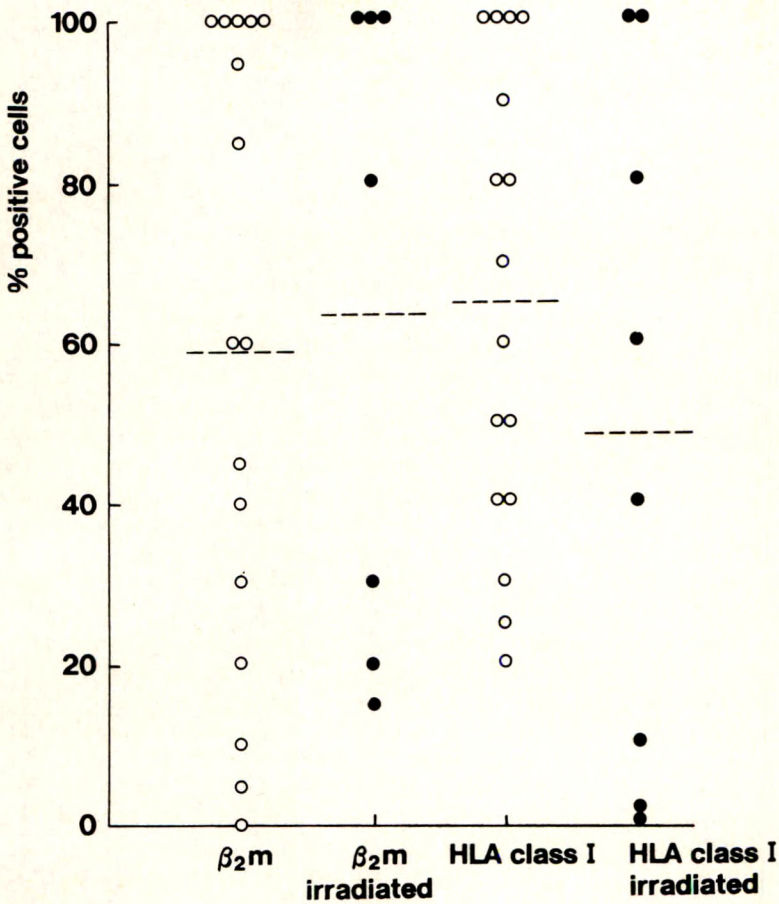


Fig. 4 (Jager and associates). Tumors without (open circles) and with (closed circles) preenucleation radiation, showing similar levels of HLA class I antigen expression. Dotted lines indicate averages.

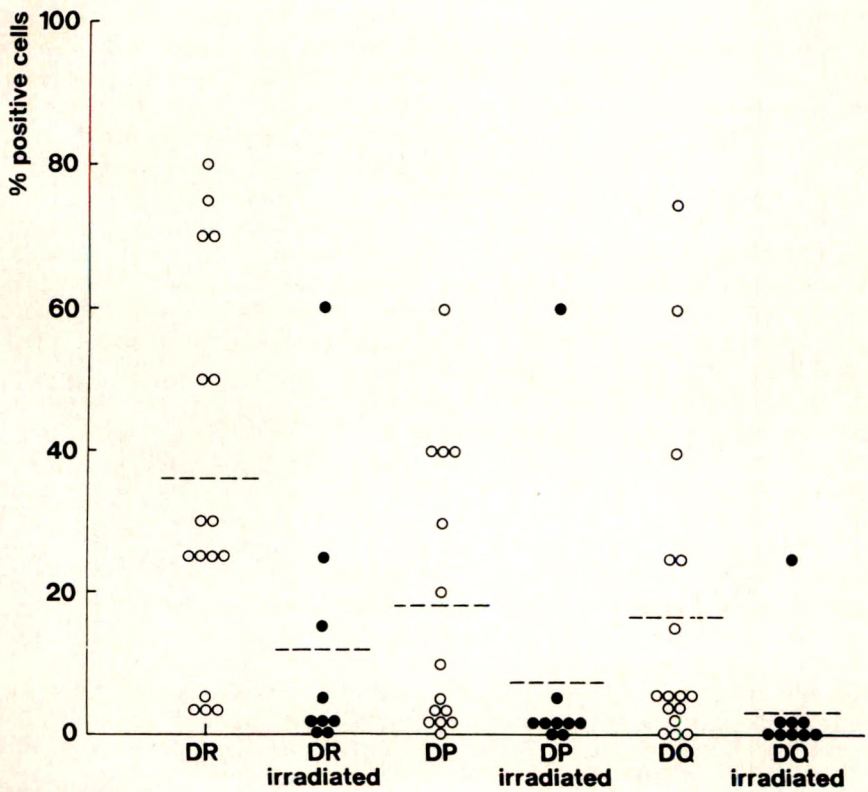


Fig. 5 (Jager and associates). Tumors without (open circles) and with (closed circles) preenucleation radiation, showing different levels of HLA class II antigen expression. Because of lack of tissue some tumors were not tested with all monoclonal antibodies. Dotted lines indicate averages.

TABLE 3
CORRELATIONS BETWEEN HLA CLASS II EXPRESSION AND CLINICOPATHOLOGIC FACTORS

	HLA-DP	HLA-DQ	INFILTRATE	RADIOTHERAPY
HLA-DR	0.000	0.001	0.082	0.003
HLA-DP	×	0.000	0.007	0.021
HLA-DQ		×	0.001	0.006
Infiltrate			×	0.000

expression of HLA class I and II antigens could be observed. Only expression of DQ and not of class I, DR, or DP was associated with the presence of a lymphocytic infiltrate. This was primarily caused by several tumors that did have a local infiltrate but did not express the antigens involved on most of the tumor cells. In such tumors, a local class II positive reaction (on 3% to 5% of the tumor cells) could be observed around vessels and around lymphocytic cells. These findings suggest that some relationship exists between the presence of an infiltrate and expression of at least one of the class II antigens in uveal melanomas.

An interesting coincidental finding was the lower level of expression of all three class II antigens in the eyes that had received irradiation before enucleation (Fig. 4). Samples from irradiated tumors were obtained from one center, and no differences in methods of enucleation or treatment of the specimens were noticed between centers. Since irradiated and nonirradiated tumors showed the same expression of β_2-microglobulin, class I, and various melanoma-associated antigens,[20] we think that sampling errors or selection bias probably do not play a role here. Although only a relatively small number of tumors was tested, our data indicate that preenucleation radiotherapy may reduce the expression of HLA class II antigens.

The observed influence of irradiation may be caused by a direct influence on tumor cells or indirectly by an effect on lymphocytes. A distinct difference in the extent of lymphocytic infiltrate was observed between irradiated and nonirradiated tumors. Whereas in the total material (25 tumors) the association between presence of infiltrate and of DP and DQ expression was significant, the association between infiltrate and DR expression was not. This may be because several nonirradiated tumors that lacked infiltrate were markedly positive for DR, while they lacked DP and DQ. The expression of HLA-DR could therefore also be related to the process of malignant transformation per se, and irradiation might abrogate the production of HLA glycoproteins. Preliminary data on HLA expression after irradiation of Epstein-Barr virus transformed B cell lines do not support a direct influence of irradiation (personal communication, F. H. J. Claas, M.D., Department of Immunohaematology and Bloodbank, University Hospital, Leiden, The Netherlands). Conversely, lymphocytes produce interferon, which stimulates expression of HLA class II antigens on all kinds of cells, for example, on melanoma cell lines.[24] Transplantation experiments with melanoma cells into nude mice also support this view: class II positive melanoma cell lines lost their class II expression after implantation in these mice, which lack the specific lymphokines that could stimulate HLA expression.[25] Reduction of lymphocytic infiltration by irradiation may lead to a decrease in stimulation of HLA class II expression. Since an association exists between irradiation, absence of lymphocytic infiltrate, and lack of HLA-DQ and -DP antigens, we favor the hypothesis that in choroidal melanoma, lymphocytes stimulate expression of HLA class II antigens on tumor cells.

It may be that the level of HLA-antigen expression in uveal melanomas will become immunologically relevant only after extraocular growth of the tumor: it was observed that patients whose melanoma had penetrated the sclera had a higher cellular and serologic reactivity against the tumor cells in vitro.[26] This could suggest that scleral penetration makes recognition by the immune system possible, since recognition depends on the presence of HLA class I and II antigens. However, in our study we did not find any correlation between HLA expression and scleral invasion. Since recognition by T cells of all antigens, including tumor-specific antigens, is probably HLA-dependent, not only the immune response to HLA antigens but to all antigens may vary with the level of HLA antigens on the tumor. It may be worthwhile to compare cellular and serologic reactivity against uveal melanomas with the level of expression of HLA and tumor-associated antigens on melanoma cells. It may also be interesting to study the absence or presence of an infiltrate in tumors after ruthenium application. However, the influence of ionizing irradiation on the immune system is complex.[27] In general, irradiation causes a decrease in resistance, for example, against pathogens and transplanted grafts. For instance, total body irradiation is used to prevent graft vs host reactions after bone marrow transplanta-

tion. One observation that irradiation may affect class II expression was described,[6] that is, a decrease in expression of class II on mouse kidneys was found after total body irradiation of the mice. T-cell activation occurs after contact between T cells and macrophages or other antigen presenting cells, carrying both class II and antigen on their surface.[10] Irradiation may decrease expression of HLA class II antigens and therefore lower immunologic recognition in a manner similar to corticosteroids and cyclosporine, both of which decrease expression of HLA class II antigens.[27] It may be worthwhile to study the expression of HLA class II antigens on lymphocytes and in normal tissues of irradiated patients. We suggest that not only the direct influence of irradiation on lymphocytes but also the effect of lymphocytes on HLA expression may contribute to the increased sensitivity of irradiated individuals to infections. The abrogation of HLA class II antigen expression by ionizing irradiation offers a new explanation for the immunosuppressive effect of irradiation. Irradiation of melanomas may have a destructive effect on dividing cells or influence immunologic recognition. Which factor has more influence on the tumor will require careful follow-up to determine a possible influence of irradiation on uveal melanomas and prognosis.

Acknowledgment

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OPHTHALMIC MINIATURE

She had the misfortune, on one of these pilgrimages during which she did not like to be disturbed, to meet on the beach a lady from Combray, accompanied by her daughters. Her name was, I think, Mme. Poussin. But among ourselves we always referred to her as "Just You Wait," for it was by the perpetual repetition of this phrase that she warned her daughters of the evils that they were laying up for themselves, saying for instance if one of them was rubbing her eyes: "Just you wait until you go and get ophthalmia."

Marcel Proust, *Remembrance of Things Past*
Translated by C. K. Scott Moncrieff and Terence Kilmartin
New York, Random House, 1981

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LETTERS TO THE JOURNAL

Respiratory Arrest After Two Retrobulbar Injections

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Respiratory arrest after retrobulbar injection of anesthetic is usually associated with bupivacaine or in combination with lidocaine.[1,2] Reports of respiratory arrest after a second retrobulbar injection are rare.

A 52-year-old woman was admitted for cataract surgery. A retrobulbar injection of 3 ml of 2% lidocaine and hyaluronidase was administered into the intraconal space of the left eye, with the eye in the upgaze position. Two minutes later, the patient lost consciousness and became apneic. Her systolic blood pressure dropped to 90 mm Hg and her heart rate decreased to 50 beats per minute. Pure oxygen was administered through a face mask and the patient's vital signs improved. Spontaneous respiration began to return within ten minutes and at 12 minutes the patient was maintaining all vital signs unaided. The patient completely recovered within two hours, but the operation was postponed. Computed tomography of the orbits showed no structural abnormality.

Six weeks later uneventful cataract surgery was performed using general anesthesia. Postoperatively the patient developed an iris prolapse, which was repaired under local anesthesia at the patient's request. After an injection of 3 ml of 2% lidocaine and hyaluronidase into the intraconal space, the patient again became unconscious and apneic. The patient responded promptly to 100% oxygen by face mask and breathed spontaneously after ten minutes. Total ophthalmoplegia was present and the prolapse was repaired. Final visual acuity was 20/30.

The absence of any bony or soft tissue abnormality on computed tomography ruled out the possibility of a small encephalocele. Therefore, access to the brain stem must have been via the meningeal sheath of the optic nerve. Kobet[2] described respiratory arrest after an initial retrobulbar injection of anesthetic. He found significant levels of anesthetic in the cerebrospinal fluid of his patient and concluded that this was the result of a direct intrathecal injection. A second retrobulbar injection was uneventful. Drysdale[3] showed the passage of dye into the subarachnoid space after retrobulbar injection. The absence of orbital hemorrhage or optic nerve damage in our patient suggests that only the meninges were traumatized by the needle tip.

During the injections, the eye was directed superonasally (the Atkinson position). Unsold, Stanley, and De Groot[4] monitored the entry of a retrobulbar needle tip during computed tomography. They noted an increased susceptibility of the structures in the posterior orbit when the eye was in upgaze. Because it is more taut when directed superonasally, the optic nerve is more likely to be impaled by the advancing needle tip. Therefore, retrobulbar injection with the eye in the primary position should cut down the risk of accidental meningeal perforation.

A variety of alternative agents are used for retrobulbar injections, including corticosteroids and alcohol. Intrathecal injection of these agents is potentially lethal.

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Acute Psychosis Associated With Topical Cyclopentolate Hydrochloride

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Temporary acute psychosis has been associated with instillation of cyclopentolate hydrochloride into the eyes.[1-4] To avoid this side effect, Havener[4] recommended a therapeutic concentration of an intitial drop of 0.5% cyclopentolate hydrochloride instilled into each eye and repeated five minutes later. We studied a case of acute psychosis after instillation of cyclopentolate hydrochloride at the recommended concentration.

A healthy 7-year-old boy came to our institution for a routine ophthalmic examination. He had no history of mental illness. Before testing his cycloplegic refraction, one drop of 0.5% cyclopentolate hydrochloride was instilled into each eye. This was repeated after five minutes. Approximately 35 minutes later, the patient jumped up and moved toward the exit. His parents persuaded him to sit in a chair, but he became restless and was unable to sit quietly. The patient became confused and disoriented, and began making "funny faces." When asked to state his name, he asked for "Campa Cola." He did not recognize his parents. Results of an immediate psychiatric examination showed that the patient was experiencing visual and tactile hallucinations, as well as severe memory loss. His speech became nonsensical and incoherent. Four hours later, all of his symptoms had disappeared. He had no recollection of the event.

Our patient's reaction prompted us to evaluate the efficacy and safety of cyclopentolate hydrochloride for refraction. We studied 50 children younger than 8 years of age. After an initial psychiatric examination, each child was tested for cycloplegic reaction using Havener's recommended dosage of cyclopentolate hydrochloride. Of the 50 patients studied, two (4%) developed an acute psychosis reaction after cyclopentolate hydrochloride instillation; 48 of 50 patients (96%) had no side effects.

These findings seem to support the efficacy of using cyclopentolate hydrochloride for testing cycloplegic refraction. However, clinicians should be aware that psychotic side effects can occur and that caution should be exercised.

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Ocular Examination Before Initiation of Lovastatin (Mevacor) Therapy

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Lovastatin is a potent inhibitor of hydroxymethylglutaryl-coenzyme A reductase, an enzyme that catalyzes an early rate-limiting step in cholesterol biosynthesis. It has recently

been released in the United States for the treatment of increased serum cholesterol levels. Because this agent is usually well tolerated and highly effective in lowering low-density lipoprotein cholesterol concentrations,[1] it may become widely used for the treatment of hypercholesterolemia. Although the overall prevalence of lenticular opacities in patients treated with lovastatin did not increase during premarketing clinical trials, and no causal relationship between lovastatin and lens change has been established (package insert, Merck Sharp & Dohme Laboratories), cataracts have been produced in some dogs given at least 50 times the maximum human dose for prolonged periods.[1] Therefore, as a precaution, the manufacturer recommends slit-lamp examination before or shortly after starting treatment with lovastatin, and annually thereafter. The reason in part for this concern dates back some 25 years to when triparanol (MER-29, an unrelated late-stage cholesterol synthesis inhibitor developed by another laboratory) was withdrawn from the market because of significant human cataract formation.[2]

The initial examination for patients receiving lovastatin should include an examination with dialted pupils and study of the lens, including retroillumination. The patients should be examined annually, with special attention directed to the anterior capsule shagreen and anterior subcapsular cortical region, especially in the periphery.

Over a three-year period, I examined 175 patients treated with lovastatin. Although I did not observe a high incidence of lens changes in these patients, I was surprised at the normal variation in the human lens, regardless of the influence of this drug. (This is especially true of the appearance and disappearance of vacuoles.) I believe that it will be a number of years, however, before lovastatin is proved or disproved as a weak cataractogenic agent.

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Familial Keratoconus

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Keratoconus is a progressive, noninflammatory disorder characterized by ectasia, protrusion, and thinning of the cornea. Although most cases of keratoconus are not hereditary, a family history of keratoconus may be noted in approximately 6% of patients.[1]

A 14-year-old boy was referred to us for corneal examination. Keratoconus had been diagnosed when the patient was 11 years old. On examination, large, irregular cones on the cornea were observed, with marked thinning and scarring centrally. Automated keratometry showed a reading of R.E.: 58.25/67.62 and L.E.: 51.00/84.50. Because of poor vision, the patient had a corneal transplant in his left eye at the age of 14 years. He had a subsequent corneal transplant in his right eye two years later.

Bilateral keratoconus had been diagnosed in the patient's 35-year-old father when he was in

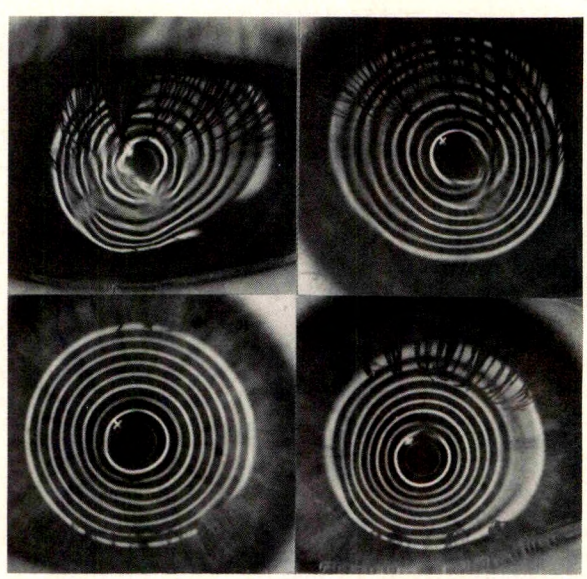


Figure (Forstot and associates). Corneal topography of parents. Top left, father's right eye; top right, left eye. Bottom left, mother's right eye; bottom right, left eye.

his 20s. Examination disclosed more advanced keratoconus in the right eye than in the left eye. Keratometry was not possible in either eye because of the severe irregularity of the corneal shape, although corneoscopic photographs were obtained (Figure, top). Bilateral keratoconus had also been diagnosed in the patient's 35-year-old mother when she was 27 years old. Results of corneal examination showed the keratoconus to be more advanced in the left eye than in the right eye (Figure, bottom).

Results of a recent clinical and epidemiologic study have estimated the prevalence rate of keratoconus in humans to be 54.5 per 100,000.[1] Previous studies have estimated the prevalence rate to be between 50 and 230 per 100,000.[2] Keratoconus is clearly an extremely rare condition, and the probability that both a husband and wife would have keratoconus is extremely small.

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Horner's Syndrome Associated With Carotid Artery Atherosclerosis

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Postganglionic Horner's syndrome and ipsilateral headache in the absence of other neurologic signs is regarded as a benign condition. It has been associated with a number of disorders of the carotid artery, including dissection, occlusion, aneurysm, and carotid body tumor.[1] We studied a case of Horner's syndrome and ipsilateral headache associated with severe atherosclerosis of the carotid artery bifurcation.

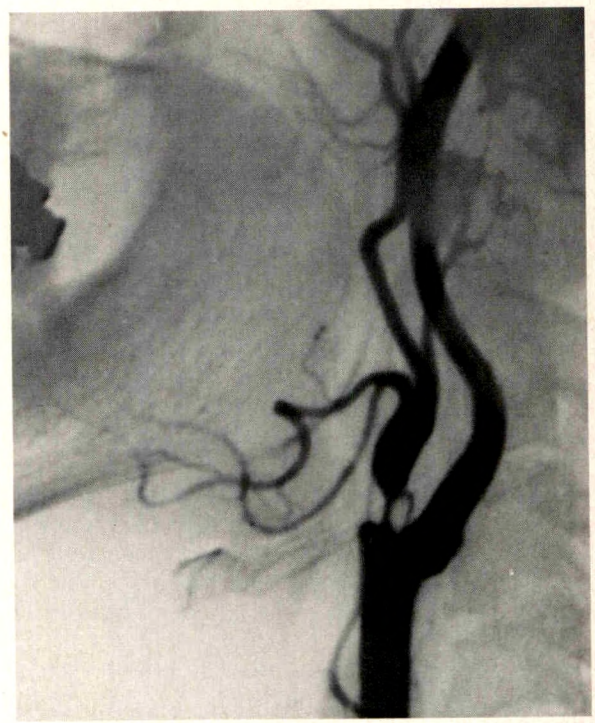


Figure (Monteiro and Coppeto). Results of an arteriogram showing severe stenosis of the left external carotid artery and the ulcerated plaque in the left internal carotid artery near the bifurcation.

A 56-year-old woman was awakened by severe pain around the left eye and temple. The pain was steady and lasted for approximately one hour. Soon afterward, she noticed that the left eyelid drooped and that the left pupil was smaller than the right. She had had a thyroidectomy at the age of 32 years because of hyperthyroidism. There was no history of migraine. The patient's hypertension was controlled with 60 mg of propranolol hydrochloride twice daily and 100 mg of hydrochlorothiazide once a day.

On examination, 2 mm of blepharoptosis was noted in the left upper eyelid, as was 1.5 mm of miosis. In moderate lighting, the right pupil measured 4.5 mm and the left pupil measured 3.0 mm. Visual acuity was 20/20 bilaterally. Both pupils reacted normally to light and near, but the left pupil dilated slowly in the dark. Although one drop of 1% hydroxyamphetamine hydrobromide dilated the right pupil to 6 mm in 30 minutes, it had no effect on the left pupil, indicating oculosympathetic damage of the third neuron. Results of the rest of the examination were normal.

Results of both a general physical examination and a neurologic examination disclosed an intense systolic bruit over the left cervical carotid artery. Results of an arteriogram showed severe stenosis of the left external carotid artery at its origin, and an ulcerated plaque in the left internal carotid artery near the bifurcation (Figure). The patient was treated with 500 mg of aspirin twice a day. Although the Horner's syndrome remained unchanged, the pain did not recur.

The vascular supply to the superior cervical ganglion is produced by the ascending pharyngeal artery (a branch of the external carotid artery), and by variable contributions from both the small branches of the carotid artery and the superior thyroidal artery (an early branch of the external carotid).[2] Havelius and Hindfelt[3] suggested that the vascular supply of postganglionic sympathetic fibers may be provided by small direct branches of the internal carotid artery.

We believe that the oculosympathetic paresis and the headache in our patient resulted from ischemia to either the superior cervical ganglion or the postganglionic sympathetic fibers. The ischemia resulted from the severe atherosclerotic disease present in both the external and the internal carotid arteries, near the bifurcation of the common carotid. Sears, Kier, and Chavis[4] produced Horner's syndrome in rabbits by ligating the vascular supply to the superior cervical ganglion. They suggested that ischemia of the sympathetic pathways could account for Horner's syndrome in humans.[4] Our findings support this hypothesis.

Grimson and Thompson[1] have divided patients with postganglionic Horner's syndrome and ipsilateral headache into three groups. Group I includes patients with hemicrania, ipsilateral oculosympathetic paresis, and parasellar involvement of the third, fourth, fifth, and sixth cranial nerves. These signs indicate a parasellar lesion and warrant an intensive neuroradiologic investigation. Group II consists of patients with typical cluster headache. Group III includes patients with headache pain not associated with typical cluster headache, as in our patient. Patients in Group III may also have involvement of the first division of the trigeminal nerve. Grimson and Thompson also pointed out that although the latter two groups share a benign condition, a carotid angiogram should be obtained for Group III patients if their headaches do not resolve within several months.[1] Our findings support this in that even in the presence of a transient, self-limited headache, severe carotid artery occlusive disease was present.

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Scintillating Scotoma After Retinal Detachment Surgery

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Scintillating scotoma has classically been associated with ophthalmic migraine. I studied two cases of scintillating scotoma apparently caused by subretinal fluid, which was slowly resorbing, after retinal detachment surgery.

Case 1

A 33-year-old myopic man underwent a scleral buckling procedure for retinal breaks. Demarcation lines were observed. Complete drainage of the subretinal fluid was not possible during surgery because extremely viscous subretinal fluid was present. Postoperatively, an area of loculated subretinal fluid posterior to the buckle was noted in the midperipheral and inferotemporal regions. The patient reported almost constant "sparkling," or scintillating, lights in the superior nasal visual field. The patient reported the scintillation in both light-adapted and dark-adapted settings. Six months later, the subretinal fluid resolved and the patient reported no further scintillating symp-

toms. Results of visual field examination showed resolution of the scotoma in this area.

Case 2

A 28-year-old woman underwent a scleral buckling procedure for retinal detachment because of lattice degeneration with holes in the inferotemporal quadrant. There were demarcation lines at the posterior aspect of the detachment that extended almost to the macula. The patient underwent a scleral buckling procedure without drainage of subretinal fluid. Three weeks after surgery, the patient complained of a scintillating scotoma in her nasal midperipheral visual field. This corresponded to a temporal area of loculated subretinal fluid posterior to the buckle. The patient learned she was pregnant at about this time. Six months later, the patient reported that the scintillating scotomas were no longer present. On examination the nasal visual field defect had disappeared and the subretinal fluid was no longer present.

In both of these cases, the retinal detachments had demarcation lines and were caused by inferior retinal holes and lattice degeneration in young patients. The subretinal fluid, which was extremely viscous in the patient who underwent drainage, was thought to be similarly viscous in the other patient. This viscosity accounts for the slow resolution of the subretinal fluid. Why stimulation of the retina resulted in the scintillating scotomas in these patients is not known. Differentiation from scintillation associated with migraine is not a problem, however, because of the clinical setting in which it occurs.

Solar Retinopathy in Persons on Religious Pilgrimage

Glen C. Cangelosi, M.D., and David A. Newsome, M.D.

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Visual disturbance from sungazing associated with religious practices or eclipse viewing has been known since ancient times.[1] Symptoms include central scotomas, blurred vision, and metamorphopsia. Results of fluorescein angiograms can appear normal, despite the presence of early white to yellow retinal lesions that occur before permanent pigment epithelial changes. Although visual recovery is usual, it is not certain.[1,2]

Recently, six children in Medjugorje, Yugoslavia reported witnessing an apparition of Mary, the Mother of Jesus. This event has stimulated worldwide pilgrimages to Medjugorje to witness the phenomena associated with the apparition, such as spinning, jumping, and pulsating movements of the sun. The sun has also been reported to emit various colors, and is occasionally covered by a dark disk. Anecdotal reports of prolonged sungazing without noticeable visual effects have appeared in the local media of Medjugorje.

We recently examined three patients who developed various degrees of solar retinopathy after sungazing during a pilgrimage to Medjugorje. Two of our three patients recovered vision fully, but the third had what appeared to be, after nine months of follow-up, permanent visual loss (Figure). All patients were prescribed 200 mg of ibuprofen twice daily and 1% prednisolone acetate four times daily for periods of one to four months. One patient also received 40 mg of oral corticosteroids for one week.

In our patients, as in nearly all reported cases of solar retinopathy, at least some improvement in visual acuity was noted. If a normal angiogram and an initial visual acuity of 20/50 or better are present on examination, prognosis is somewhat favorable, regardless of any visible lesions. Hypopigmentation of the pigment epithelium developing at various times after the sun exposure was observed. This was most prominent in the patient who reported repeated sungazing episodes. Despite the effects on the retinal pigment epithelium of repeated and longer exposure to sunlight,[3] the acuity of two of our patients returned to preexposure levels, whereas the third patient experienced loss of vision after only one sungazing episode. We treated these patients with corticosteroids and nonsteroidal, anti-inflammatory drugs on an empiric basis. Because the natural course of solar retinopathy is to show resolution and visual improvement, it is unclear whether the therapy hastened the resolution in our patients.

We wish to reemphasize the potential for permanent loss of vision after sungazing. Pilgrims to Medjugorje have repeatedly claimed to have stared at the sun with both eyes for

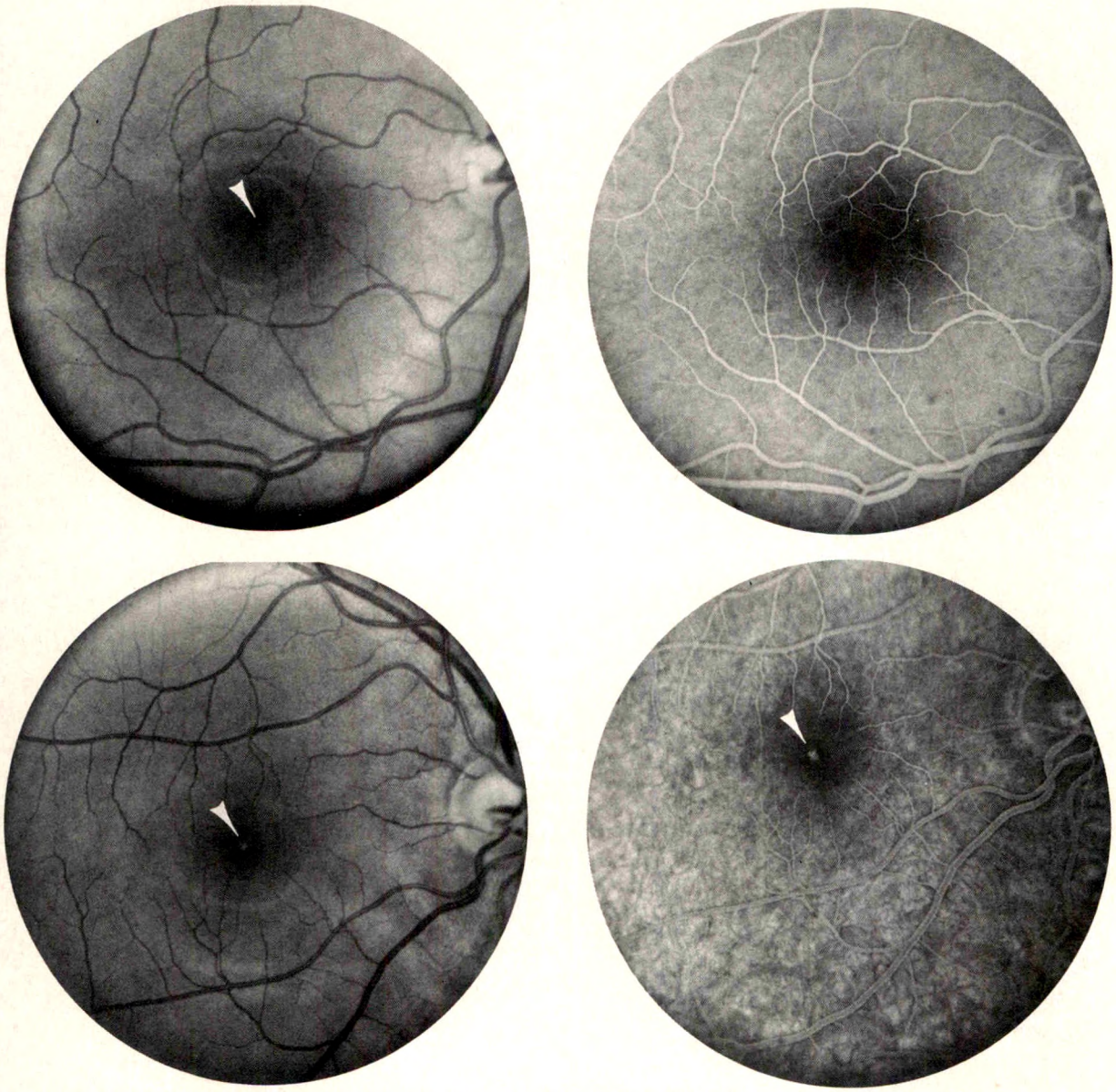


Figure (Cangelosi and Newsome). Top left, Fundus photograph of the right eye of a 21-year-old woman, taken 21 days after sungazing on pilgrimage and several brief episodes of sungazing in New Orleans. Note the focal yellow exudate-type lesion within the retina near the center of the fovea (arrowhead). Both eyes looked similar. Fluorescein angiography of the right eye was normal at the time this lesion was present, as well as nine months (top right) after the sungazing episodes. Visual acuity eventually improved from 20/50 to 20/20 bilaterally. Bottom left, Fundus photograph of the right eye of a 26-year-old man, also taken 21 days after sungazing on pilgrimage. Note the circumscribed lesion, which is represented by a window defect on fluorescein angiography (bottom right). The patient's visual acuity improved from 20/80 to only 20/30.

periods in excess of ten minutes with no symptoms or apparent ill effects. This contrasts with well-documented reports of solar retinopathy occurring after less than 60 seconds of sungazing.[2] The effects of the time of day and atmospheric filtration of sunlight may play a role. Sungazing is not known to raise the temperature of retinal tissues sufficiently to cause thermal damage, implicating a short-wavelength-dependent photochemical toxic mecha-

nism.[4] Sungazing in Medjugorje reportedly often occurs near sunset, thus possibly reducing but not eliminating the hazard.[5]

Our recent experience demonstrates that the general public is not completely aware of the hazards of sungazing, including possible visual loss. Despite personal beliefs, those who gaze at the sun risk permanent retinal damage.

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Dye Yellow Photocoagulation of Retinal Arterial Macroaneurysms

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We treated five macroaneurysms with dye yellow light (577 nm) over the past three years. In treating vascular structures, this dye yellow wavelength is useful because it has excellent absorption in oxyhemoglobin and a high hemoglobin-to-melanin absorption ratio, which minimizes retinal pigment epithelium damage.[1]

The objective of macroaneurysm laser therapy is to reduce leakage and the probability of rupture, without occluding or perforating the underlying artery. Consideration of two principles can reduce the risk of complications. First, experimental studies have shown that laser burns placed directly on a retinal artery produce vessel wall effects distal to the treatment site.[2] This is because of light absorption and heating in the blood column, and blood flow.[2] Second, the shorter the duration of exposure, the higher the power required for a therapeutic effect, and the narrower the safety margin between photocoagulation and undesirable thermomechanical effects.[1]

The macroaneurysms were photocoagulated with 0.2- to 0.5-second exposures, a 200-μm spot size, and the lowest power setting that produced a visible lesion. Our power settings typically ranged from 90 to 130 mW, similar to those we have used in over 200 cases of dye yellow panretinal photocoagulation. Our initial burns were placed adjacent to the macroaneurysm, both for therapeutic effect and to help determine local threshold. Subsequent burns, each partially covering the macroaneurysm, were placed slightly proximal to, and then around, the macroaneurysm. One of the five macroaneurysms required a second treatment. Neither arterial perforation nor arterial occlusion occurred. Visual acuity improved in three of the five cases, all of which have been followed up for more than six months.

Russell and Folk[3] reported a case of branch retinal artery occlusion after dye yellow photocoagulation of an arterial macroaneurysm. A high power setting and a short exposure time (200 mW, 0.1 second) had been used, although several factors may have prompted these laser parameters, such as patient eye movement. Additionally, individual vascular abnormalities could have predisposed their patient to arterial occlusion, regardless of laser wavelength, exposure duration, or power setting. Their case demonstrates the difficulties associated with laser therapy for macroaneurysms. It also emphasizes the importance of selecting the lowest power needed for retinal photocoagulation in a particular patient, regardless of laser wavelength.

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Congenital Tilted Disk Syndrome Associated With Parafoveal Subretinal Neovascularization

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The congenital tilted disk syndrome is caused by defective closure of the embryonic cleft. It is characterized by inferonasal tilting of the optic disk, an associated inferonasal crescent, and thinning of the retinal pigment epithelium and choroid in the inferonasal portion of the fundus. It is usually accompanied by varying degrees of myopic or hypermetropic astigmatism and visual field defects.[1] I studied a case of bilateral congenital tilted disk syndrome associated with unilateral parafoveal subretinal neovascularization.

A 43-year-old woman was referred because of metamorphopsia and blurring in her right eye. Her visual acuity was R.E.: 20/60 and L.E.: 20/40, with a myopic astigmatism in both eyes (R.E.: -2.50 -3.50×170, L.E.: -3.00 -3.50×10). Ophthalmoscopy showed bilateral congenital tilted disks with shallow inferonasal staphylomata. In the right eye was a small serous detachment of the retina involving the fovea. The margin of the serous detachment was lined by small hard exudates, and a subretinal neovascular membrane in the inferior part of the serous detachment was noted (Figure, left). In the left eye, a small group of drusen inferior to the fovea at the border of the choroidal hypoplasia was observed. Fluorescein angiography of the right eye showed early filling of the subretinal new vessels, which did not extend into the foveal avascular zone (Figure, right). The neovascular membrane was treated successfully with confluent laser burns using the green wavelength of the argon laser.

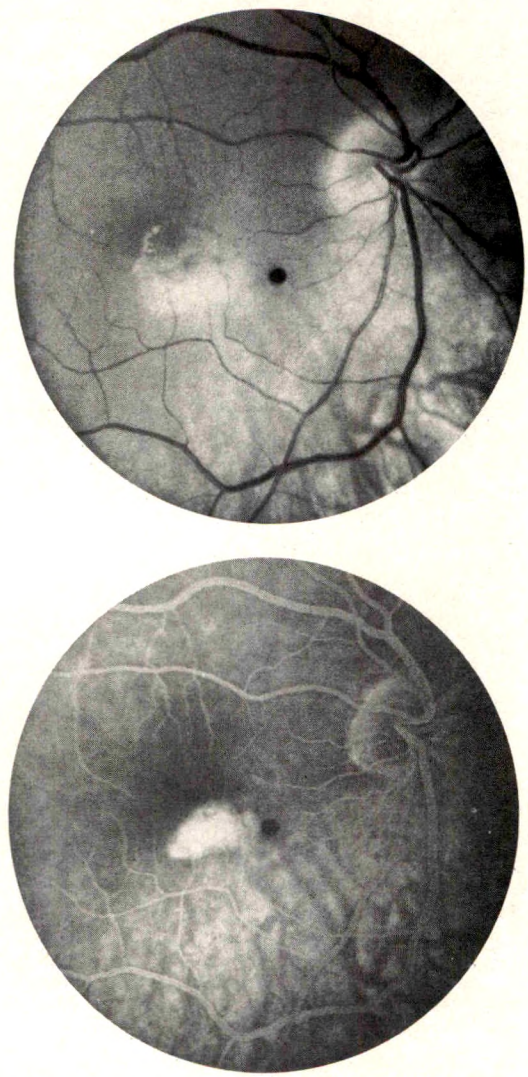


Figure (Stur). Top, Red-free photograph and bottom, fluorescein angiogram (late venous phase) of the parafoveal subretinal neovascularization inferior to the fovea at the border of the hypoplastic part of the choroid. The black spot in the center of the picture is a camera artifact.

Subretinal neovascularization can be caused by a variety of diseases.[2] These include congenital anomalies caused by defective closure of the embryonic cleft, such as retinochoroidal coloboma,[3] and pits of the optic nerve head.[4] The hypoplasia of the choroid in this disease is similar to the acquired choroidal degeneration of myopic eyes. Therefore, the parafoveal sub-

retinal neovascularization in our patient may have been caused by degenerative changes associated with congenital malformation. This conclusion is supported in that both the subretinal neovascularization and the group of drusen in the contralateral eye originated where the border between the hypoplastic and the normal choroid was adjacent to the fovea. This area may be more sensitive to secondary degenerative changes than other fundus areas.

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Surgical Treatment of Acute Glaucomatocyclitic Crisis in a Patient With Primary Open-Angle Glaucoma

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The syndrome of acute glaucomatocyclitic crisis, as described by Posner and Schlossman,[1] consists of unilateral increased intraocular pressure associated with mild conjunctival injection, blurred vision, anterior chamber flare, and small discrete keratic precipitates on the cornea. It has been associated with primary open-angle glaucoma.[2] This condition is usually self-limiting, and is treated with ocular hypotensive agents and topical corticosteroids. We studied a case of acute glaucomatocyclitic crisis in a patient with primary open-angle glaucoma, in which surgical intervention was the treatment of choice.

In 1971 a 47-year-old man complained of halos around lights, pain, blurred vision, sensitivity to light, and tearing and redness in the left eye. He had had similar recurrent symptoms for one year, and had been given a regimen of topical pilocarpine and epinephrine; he could not tolerate acetazolamide. In the left eye, intraocular pressure was 50 mm Hg and visual acuity was 20/50. Microcystic edema of the cornea, pigmented keratic precipitates, and mild flare of the anterior chamber were noted. The iridocorneal angle was open, with no peripheral anterior synechiae. The optic disk appeared healthy, with good neuroretinal rim tissue in all areas, and a cup-to-disk ratio of 0.3. There was no detectable visual field loss. Neither glaucomatous nerve damage nor visual field loss was present in the right eye, although a mild increase in intraocular pressure was noted. The patient was treated with topical epinephrine, dexamethasone, and oral dichlorphenamide. From 1971 to 1974, the patient had three more unilateral acute glaucomatocyclitic crises in the left eye. Each time he was treated with topical corticosteroids (fluorometholone or dexamethasone), oral methazolamide, and topical epinephrine. Each episode lasted three to four weeks. During the 1971 to 1974 period, the patient developed paracentral scotomas, and an increase in the cup-to-disk ratio from 0.3 to 0.7. In September 1974, a trabeculectomy with a peripheral iridectomy was performed.

In a 12-year follow-up period, there were no recurrent episodes of acute glaucomatocyclitic crisis. Intraocular pressure in the left eye ranged from 5 to 12 mm Hg and visual acuity was 20/30, with no detectable change in the visual field or the optic disk. Possible early stage primary open-angle glaucoma in the right eye remained stable on medical therapy.

The filtering surgery may have decreased the intraocular pressures associated with glaucomatocyclitic episodes by establishing an alternative outflow channel that compensated for either a decreased outflow facility or increased aqueous formation.[3]

We believe that the surgical treatment of this patient was successful, with success being defined as no further signs or symptoms, no recorded increases in intraocular pressure, and

no further visual loss or optic disk change.

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Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Limbal- vs Fornix-Based Conjunctival Trabeculectomy Flaps

EDITOR:

In the article "Limbal- vs fornix-based conjunctival trabeculectomy flaps," by Carlo E. Traverso, Karim F. Tomey, and Sobhi Antonios (Am. J. Ophthalmol. 104:28, July 1987), the authors concentrate on the length of the surgical procedure and the overall results. They concluded that there is little difference in the results of the two procedures or the time taken to perform the surgical procedures. I wish to comment on some aspects of trabeculectomy when using a conjunctivo-Tenon's flap, which I belive add to the safety of the operation.

The authors report progressive shallowing of the anterior chamber with the fornix-based conjunctival flap as compared to a deeper chamber with the limbal-based flap, although both were comparable after the first week. The progressive shallowing of the anterior chamber is related to their technique in which the limbal end of the two radial incisions of the lamellar scleral flap were left unsutured. This allows the aqueous humor to drain through the radial incision at the corneoscleral limbus; spread along the front edge of the conjunctival flap, which is tightly opposed to the sclera; and leak out at the edges of the conjunctival flap through the absorbable suture site. If the conjunctival flap is not snugly opposed to the sclera, then the aqueous humor may drain freely through the front edge of the conjunctival flap. This would cause an even higher incidence of shallow anterior chamber or even flat anterior chamber than the authors described. When a fornix-based flap is used, the presence of a shallow anterior chamber during the week after surgery can be almost totally eliminated by suturing the limbal edge of the two radial incisions.

I have found it easier to oppose directly the conjunctival flap and prevent leakage at the site of the conjunctival suture when 10-0 nylon sutures rather than absorbable sutures are used.

MAURICE H. LUNTZ, M.D.
New York, New York

Reply

EDITOR:

Dr. Luntz's observations are most appropriate and should be taken into consideration before switching from limbal-based to fornix-based conjunctival flaps for trabeculectomy. Indeed, additional sutures at the radial incisions of the lamellar scleral flap help reduce postoperative hypotony. We usually tie our sutures only at the corners of the scleral flap to obtain some drainage of the aqueous humor. Should the scleral flap be left too loose, profound postoperative hypotony and a shallow or flat anterior chamber will be likely to occur, regardless of whether the conjunctival flap is limbal or fornix-based. As appropriately pointed out by Dr. Luntz, postoperative hypotony and a shallow or flat

anterior chamber may be particularly evident when fornix-based conjunctival flaps are used, especially if the flap is sutured too loosely.

Regarding the use of nylon vs absorbable sutures, we have been pleased with the latter, probably because we have them available mounted on tapered needles. Certainly, 10-0 nylon can be a good alternative.

CARLO E. TRAVERSO, M.D.
KARIM F. TOMEY, M.D.
SOBHI R. ANTONIOS, M.D.
Riyadh, Saudi Arabia

Clinical Evaluation of the Oculab Tono-Pen

EDITOR:

In the article "Clinical evaluation of the Oculab Tono-Pen," by D. S. Minckler, G. Baerveldt, D. Heuer, B. Quillen-Thomas, A. F. Walonker, and J. Weiner (Am. J. Ophthalmol. 104:168, August 1987), the authors conclude that the differences in intraocular pressure measured by this instrument are not "clinically troublesome." Of the 270 eyes studied, intraocular pressure in approximately 39% of the eyes measured outside an error range of ±3 mm Hg. Many of these eyes had high intraocular pressures. Because surgical decisions in glaucoma are influenced by intraocular pressures, I believe that a qualification should be placed on the use of this instrument in patients with glaucoma. Although the authors found no statistically significant difference in intraocular pressure that measured greater than 24 mm Hg ($P = .30$), the error in the measurement may be clinically significant for a glaucoma patient.

The Tono-Pen may be a convenient and an accurate means for measuring intraocular pressure in uncooperative patients or in patients with irregularly shaped corneas. However, the impression that this instrument, with its "trivial differences" in measurement, can replace the Goldmann applanation tonometer in treating patients with high intraocular pressure should not be given.

EVE J. HIGGINBOTHAM, M.D.
Chicago, Illinois

Reply

EDITOR:

We appreciate Dr. Higginbotham's concern regarding our statement that the "small underestimation of intraocular pressure with the Tono-Pen in eyes with high intraocular pressure . . . is not considered likely to be clinically troublesome." That statement was based on our belief that a relatively small error (±3 mm Hg) in the majority of serial intraocular pressure measurements should not adversely affect therapy judgments in glaucoma patients. We do not believe that an error of this magnitude is clinically problematic because in the same pressure ranges, the error is barely more than the error associated with the standard Goldmann tonometer, which is at least ±2 mm Hg. Although the measurements of higher intraocular pressure may be misleading when associated with an error greater than ±3 mm Hg, intraocular pressure alone should never constitute the sole reason for clinical judgments. Regardless of the method used, any intraocular pressure measurement is an approximation, and should be evaluated in the whole context of the problem. At higher intraocular pressures, the error in measurement is likely to be greater with any instrument, including the Goldmann tonometer. We could only assume that the Goldmann measurements were accurate as they were impossible to verify.

Dr. Higginbotham's suggestion that the Tono-Pen may have special application for intraocular pressure measurements in complicated cases such as uncooperative patients or patients with irregularly shaped corneas is somewhat inconsistent with her concerns about the instrument's accuracy, since no study has yet determined the Tono-Pen's error in such cases. We predict, however, that the error rate for any instrument in a complicated case would be far greater. Therefore, judgments of therapy based on intraocular pressure measurements would be more problematic in these cases.

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DALE K. HEUER, M.D.
BETH QUILLEN-THOMAS, B.SC.
A. FRANCES WALONKER, D.B.O.
JOHN WEINER, DR.P.H.
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Nd:YAG Laser Photodisruption of the Lens Nucleus Before Phacoemulsification

EDITOR:

In the article "Nd:YAG laser photodisruption of the lens nucleus before phacoemulsification," by E. H. Ryan, Jr., and S. Logani (Am. J. Ophthalmol. 104:382, October 1987), the authors determined that laser pretreatment of the lens nucleus decreased phacoemulsification time and thus increased the safety of the procedure.

I would like to bring to the attention of the authors that Dr. Stephen Chambless and I have performed this procedure safely on over 2,000 patients. Dr. Chambless discussed this procedure in the January 1985 issue of the American Intraocular Implant Society Journal. I reported a detailed account of the procedure in the May 1987 American Society of Cataract and Refractive Surgery Journal. In the October 1987 edition of the Video Journal of Ophthalmology, I performed the technique in a video segment.

I have found that the technique is effective in decreasing the phacoemulsification time significantly. I have also found that the pretreatment of the nucleus allows one to remove many cataracts with a simple irrigation and aspiration technique, thereby bypassing phacoemulsification completely. If the laser is properly focused, one can avoid posterior capsule rupture completely.

JERRY ZELMAN, M.D.
Miami Beach, Florida

EDITOR:

I would like to congratulate E. H. Ryan, Jr., and S. Logani on their article, "Nd:YAG laser photodisruption of the lens nucleus before phacoemulsification" (Am. J. Ophthalmol. 104:382, October 1987). Their article confirms my belief that pretreatment of the lens nucleus is a valuable aid in phacoemulsification.

Perhaps the authors were not aware of a study that I presented at the American Intraocular Implant Society meeting in April 1984, and which was published in the January 1985 issue of the American Intraocular Implant Society Journal, concerning 220 cases of Nd:YAG laser pretreatment of the nucleus prior to phacoemulsification, or of the study presented by Dr. Jerry Zelman in the May 1987 issue of the American Society of Cataract and Refractive Surgery Journal concerning a larger number of cases. Additionally, they obviously were not aware of my presentation at the American Society of Cataract and Refractive Surgery meeting in Orlando in April 1987, of which approximately 1,000 cases are scheduled to be published in the American Society of Cataract and Refractive Surgery Journal in an upcoming issue, in addition to multiple articles in the "newspapers" (Ophthalmology Times, Ocular Surgery News) by Drs. Richard Keates, Jerry Zelman, and myself.

My findings differ from theirs in that I found an even greater percentage decrease in emulsification time with treated as compared to untreated nuclei, and that the effect was more marked in denser nuclei, with the greatest effect being in 4+ nuclear sclerosis; also the risk of accidental rupture of the posterior capsule is virtually zero with proper technique.

W. STEPHEN CHAMBLESS, M.D.
Dallas, Texas

Reply

EDITOR:

We appreciate the interest shown and comments made by Drs. Zelman and Chambless regarding our study.

We were aware of the reports of this procedure in the various "newspapers," but our review of publications listed in the Index Medicus failed to produce the other listings.

Our study showed that YAG photodisruption of the nucleus shortens phacoemulsification time in vitro. We think this may be a promising adjunct to cataract surgery. However, we still have several concerns about recommending this technique before routine cataract surgery.

First, capsular rupture is the most serious risk of this procedure. In the hands of experienced surgeons such as Drs. Chambless and Zelman, the capsular rupture rate is undoubtedly low. In less experienced surgeons, one would expect a higher rate of this complication. Preoperative capsular rupture potentially exposes the patient to lens-induced uveitis, increased intraocular pressure, or other unknown risks. It has yet to be proven whether the benefits of this procedure exceed the risks.

Second, the current state-of-the-art technique in posterior chamber lens implantation requires an incision of approximately 7 mm. The major advantage of phacoemulsification over the standard nucleus expression technique is thus lost. If injectable implant technology is proven safe and effective, phacoemulsification and therefore YAG photodisruption could offer more significant benefits over extracapsular cataract surgery with expression of the nucleus.

Additionally, there exists potential for abuse. An extra charge to the patient for this procedure could create a financial incentive for its overuse. Also, in this age of cataract advertising, being the first in town to do "laser cataract surgery" could be misused as a marketing tool.

This is a procedure that could be readily studied in a controlled, randomized, prospective fashion. The risks and benefits could be documented, and the indications defined. While the experiences of Drs. Zelman and Chambless suggest this is an effective procedure, their experiences remain anecdotal. We think YAG photodisruption of the lens nucleus is a promising technique, the value of which should be tested in a controlled clinical trial.

EDWIN H. RYAN, JR., M.D.
St. Louis, Missouri
SANJAY LOGANI, B.S.
Chicago, Illinois

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Informed Consent. Legal Theory and Clinical Practice. By Paul S. Appelbaum, Charles W. Lidz, and Alan Meisel. 286 pages, index. $27.95

Reviewed by G. F. Judisch
Iowa City, Iowa

This remarkable book would be an excellent core text for a course that should be mandatory in every medical school curriculum. Its message is pertinent and timely for all physicians who deal with patients.

The three authors, a psychiatrist, a sociologist, and a law professor, have collectively and individually studied the concept of informed consent for over a decade, and found the doctrine to be poorly understood. In response, they have written this comprehensive introduction to the theory and practice of informed consent. Their personal involvement and firsthand experience make the practical knowledge and clinical examples in this book especially instructive.

There are five parts. Part I addresses the origin of the concept of informed consent and the ethical theories upon which the idea is based. Part II outlines the evolution of the legal theory of informed consent with emphasis on the legal ambiguities that cause problems for practitioners. In Part III, the problems faced by health care professionals when applying informed consent theory in a clinical setting are considered, and a model is given for simplifying that task and making it clinically meaningful and therapeutically helpful. Part IV is concerned with the special problems of informed consent in research (as in clinical trials and new but unproved procedures or devices) as opposed to informed permission to treat. The long-term need to improve the practitioner's skill in satisfying ethical and legal mandates is discussed in Part V and a course of action is suggested.

The book deals with much more than informed consent. It also contains a detailed description of the doctor-patient relationship, the cornerstone of which the authors firmly believe is the right of patients to participate in the making of their own medical decisions. Most importantly, it urges that this decision-making be an ongoing process of information exchange and not an isolated event.

In a era when malpractice problems are rapidly increasing and increasing emphasis is placed on competition for patients and on cost containment (especially through health maintenance organizations, preferred provider organizations, and other types of capitation plans), it is possible that in the near future, what the patient wants may be overwhelmed by powerful economic and bureaucratic forces. This makes it essential that patients understand their situation and that genuine informed consent to treat or, perhaps more disconcertingly, not to treat be obtained for reasons other than simply to comply with legal or regulatory requirements or to guard against liability.

Considerable attention is paid to ethics, to legal theory, and to their evolution, but there is also ample concern for the realities of patient care as evidenced by frequent clinical examples that demonstrate that it is not only necessary to obtain informed consent but that considerable good will occur if done well. Interestingly, one of the more telling of these examples concerns a physician-patient's critique of his encounters with several eminent ophthalmologists.

If every physician would read and then reread this book, informed consent would soon be embraced as a pleasant and constructive dialogue guaranteed to strengthen doctor-patient relationships and improve therapeutic results. Inevitably, this would enhance the quality of life for both practitioner and patient.

Diagnosis and Management of Ocular Motility Disorders. By Joyce Mein and Brian Harcourt. Oxford, Blackwell Scientific Publications, 1986. 367 pages, index, illustrated. $85 ($8 postage and handling)

Reviewed by Otto A. Wiegmann
Brookfield, Wisconsin

This textbook is the latest entry in the field of strabismus. It reflects the cooperative effort of a team from Leeds, England: Joyce Mein, the former principal of the Orthoptic School in Leeds, and Brian Harcourt, senior consultant

from the University of Leeds. Their book is quite different from other motility publications. The material is presented in a fairly comprehensive manner and tightly organized: the main sections are divided and subdivided into shorter and shorter chapters, itemized by alphabetical and numerical order often down to single sentences. Although the reader will appreciate the sense of order and clarity, this style almost by necessity eliminates much of the reference to the pertinent literature and, without discussion, imposes a hierarchy of relative importance.

Separate chapters on anatomy and physiology have been omitted. Instead, anatomic and physiologic details are provided in connection with methods of examination, clinical features, and treatment. This juxtaposition of topographic anatomy and strictly "applied" physiology is relevant and in many ways refreshing. In the chapter on refraction in strabismus under the heading of anisometropia, I would have liked a discussion of the difference between anisohyperopia and anisomyopia in regard to binocular vision and amblyopia. Unfortunately, there is a scarcity of illustrations throughout the entire book. This should perhaps be reconsidered in further editions.

The book gives a highly organized, clearly written account of the field of strabismus. It is not a book for beginners, either in ophthalmology or in orthoptics. Its strength is clarity and order. For those who are familiar with the field, it provides a solid and detailed review, in which the voice of the experienced orthoptist can be heard.

Ophthalmic Technology. A Guide for the Eye Care Assistant. Edited by Stephen J. Rhode and Stephen P. Ginsberg. New York, Raven Press, 1987. Softcover, 508 pages, index, illustrated. $39

Reviewed by Reed N. Bouchey
Iowa City, Iowa

The training of ophthalmic medical assistants was always a patchwork affair. It consisted mostly of practical, hands-on, clinical demonstration and experience, supplemented occasionally with bits and pieces of useful information from ophthalmic texts.

Stein and Slatt's book, "The Ophthalmic Assistant," published in 1968, is still the cornerstone upon which ophthalmic education for medical assistants rests today. No serious competitor has come along until now.

The editors of "Ophthalmic Technology" have provided a worthwhile text suitable for use as a reference work or as a core manual in the education of ophthalmic assistants. The first half of the book approaches ocular anatomy and physiology from a clinical point of view. The second half covers a wide range of diagnostic tests and clinical skills from electroretinography to opticianry. A welcome addition to this text is the first chapter, which explains the differing roles of the ophthalmic assistant, ophthalmic technician, and ophthalmic technologist, and outlines the requirements for certification for each position. As further editions are published this textbook will undoubtedly be polished until it gives Stein and Slatt some healthy competition.

The book's hidden value may be in what it can do for beginning ophthalmology residents who crave the little bits of practical information that are hard to find in general ophthalmology textbooks.

Nursing Care of the Eye. By Heather Boyd-Monk and Charles G. Steinmetz III. East Norwalk, Connecticut, Appleton & Lange, 1987. Softcover, 358 pages, index, illustrated. $35.95

Reviewed by Sarah C. Smith
Iowa City, Iowa

This book is a comprehensive guide for both the veteran ophthalmic nurse and the new practitioner. The general eye care section is full of frank practical advice and gives the reasons for each procedure and test. The things that ophthalmic nurses do are presented concisely and thoughtfully along with the discussion of each kind of ocular problem, and the things the nurse should tell the patient are appropriately stressed throughout the book.

It is a great book, comprehensive, authoritative, and written with care and insight. Every ophthalmic nurse should have a copy at hand.

Oxford Textbook of Medicine, ed. 2. Edited by D. J. Weatherall, J. G. G. Ledingham, and D. A. Warrell. New York, Oxford University Press, 1987. Illustrated, index. $135 (two volume set)

Reviewed by FRANK W. NEWELL
Chicago, Illinois

These two volumes have some 350 contributors and provide a host of authoritative reviews. The books are definitely not intended for transport, inasmuch as their 3,800 pages weigh 16 pounds. The volumes are divided into 28 sections together with an appendix of values for biochemical data. Each of the two volumes contains the usual front matter and a complete index. The chapters are interesting and provocative with many having a more philosophic orientation than one finds in American textbooks. The references are current (some as late as 1986). This is a fine reference for the office.

Books Received

Work, Aging, and Vision. By Working Group on Night Vision, Committee on Vision, Commission on Behavioral and Social Sciences and Education, and National Research Council. Washington, D.C., National Academy Press, 1987. Softcover, 67 pages, illustrated. $11.50 (U.S., Canada, Mexico) $14.25 (Export)

This is a report of a conference on the issue of keeping older workers in the work force as long as possible despite the many changes in vision that occur with age (smaller pupil size, loss of focusing ability, cataracts, macular degeneration, glaucoma). The 48-page narrative report is followed by an annotated bibliography.

Glaucoma Update III. Edited by G. K. Krieglstein. New York, Springer-Verlag New York, Inc., 1987. Softcover, 270 pages, index, illustrated. $80.60

This text documents the proceedings of the third meeting of the Committee on Glaucoma of the International Congress of Ophthalmology. Thirty-seven research papers on all aspects of glaucoma are included.

A Guide to Learning Disabilities: A Report to the U.S. Congress. Office of Research Reporting, National Institute of Child Health and Development. 230 pages. No charge

This guide is published by the Department of Health and Human Services. They describe it as "the first comprehensive assessment of the prevalence, causes, diagnosis, treatment and prevention of learning disabilities." The report summarizes a January 1987 conference of 13 federal health agencies within the congressionally mandated Interagency Committee on Learning Disabilities. It is available without charge from the Office of Research Reporting, National Institute of Child Health and Development, P.O. Box 29111, Washington, D.C. 20040; tel. 301/496-5133. (The proceedings of the conference are scheduled for later publication.)

Reviews in Neurology and Ophthalmology. Edited by J. T. W. Van Dalen. Amsterdam, Aeolus Press, 1987. 160 pages, index, illustrated. $45

Nine reviews from the journal "Neuro-Ophthalmology" are reprinted in this volume. Many have been updated, and this reprinting should make them more accessible.

Manual of Cataract Surgery. By Robert M. Sinskey and Jay V. Patel. New York, Churchill Livingstone, Inc., 1987. Softcover, 99 pages, index, illustrated. $30

This is a short and easy-to-read manual of cataract surgery that emphasizes the most pertinent aspects of each step of the surgical procedure.

ABSTRACT DEPARTMENT

Edited by David Shoch, M.D.

Acta Endocrinologica

The specificity of autoantibodies in Graves' ophthalmopathy. Kendall-Taylor, P., Jones, D., and Atkinson, S. (Royal Victoria Infirm., Newcastle upon Tyne, NE1 4LP, U.K.). Acta Endocrinol. 281(suppl.):330, 1987.

The characteristic orbital change in Graves' ophthalmopathy is an enlargement of the extraocular muscles. Autoantibodies to these muscles have been found in patients with Graves' ophthalmopathy. However, the autoantibody also binds to skeletal muscle antigen. This raises questions as to why only extraocular muscles enlarge and not other muscles in the body. Myosin and actin have been excluded as responsible antigens. The authors believe that the antigen is also distinct from thyroid antigens. They have not been able to establish this in the small group of patients with which they worked. (3 figures, 2 tables, 5 references)—David Shoch

Acta Ophthalmologica

Capsule thickness of cataractous lenses with and without exfoliation syndrome. Ruotsalainen, J., and Tarkkanen, A. (Dept. Ophthalmol., Helsinki Univ. Gen. Hosp., Haartmaninkatu 4C, SF-00290 Helsinki, Finland). Acta Ophthalmol. 65:444, 1987.

Forty of 105 cataractous lenses removed intracapsularly had exfoliation. There was no statistical difference in thickness between the lenses with and without exfoliative material. Because the central portion of the posterior capsule is so thin, great care is needed during polishing as part of extracapsular cataract surgery. The higher operative complication rate in eyes with the exfoliation syndrome probably occurs because the zonules are more friable. (6 figures, 5 tables, 9 references)—David Shoch

Annals of Neurology

Still another cause of monocular oscillopsia. Rosenberg, M. L. (Dept. Neurol., Uniformed Svcs. Univ. of the Health Sci., Bethesda, MD 20814-4799). Ann. Neurol. 22:97, 1987.

A patient noted intermittent vertical diplopia with vertical oscillation of one of the images. He associated this with repetitive twitching of the upper eyelid that occurred only when he was wearing contact lenses. Apparently, the movement of the eyelid caused the contact lens to oscillate and induced a secondary monocular oscillopsia. Eyelid myokymia in a contact lens wearer should be added to the differential diagnosis of unilateral oscillopsia. (1 reference)—David Shoch

British Journal of Dermatology

Galactose tolerance in patients with atopic cataracts. Muhlemann, M. F., Mount, J. N., and Cream, J. J. (Dept. Dermatol., Charing Cross Hosp., London W6 8RF, U.K.). Br. J. Dermatol. 117:37, 1987.

Galactosemia has been suggested as a contributory factor in the pathogenesis of some early onset and age-related cataracts. To assess whether galactosemia plays a role in the development of atopic cataracts a galactose tolerance test was carried out in eight patients with atopic dermatitis whose cataracts had appeared between the ages of 12 and 39 years. In seven patients the galactose tolerance test was normal and in one the test was slightly abnormal. Impaired galactose tolerance appears to have no role in the pathogenesis of atopic cataract. (1 table, 18 references)—David Shoch

British Journal of Ophthalmology

Cataract: the relation between myopia and cataract morphology. Brown, N. A. P., and Hill, A. R. (63 Harley St., London W1N 1DD, England). Br. J. Ophthalmol. 71:405, 1987.

One hundred British patients were studied in whom the refractive error was known four years before the development of cataract. Refractive error was also known four years earlier for the age-matched controls. The study showed that simple myopia did not appear to predispose to cataract. The refractive change toward myopia observed in patients with cata-

ract was caused by the development of the cataract itself, particularly nuclear sclerosis. Patients more than 55 years of age who showed a myopic change of refraction had a high probability of developing a nuclear sclerotic cataract. Eyes with cortical cataract or subcapsular cataract without nuclear sclerosis showed a gradual hypermetropic change with time, as does the healthy aging eye. (7 figures, 7 tables, 22 references)—David Shoch

Canadian Medical Association Journal

Toxic ocular effects of ethambutol. Kahana, L. M. (604-25 Charlton Ave. E., Hamilton, Ontario, Canada L8N 1Y2). Can. Med. Assoc. J. 137:213, 1987.

In four patients receiving ethambutol who developed serious visual loss, three had received only 15 mg/kg of body weight/day. The fourth patient was given 25 mg/kg of body weight/day for four months. Of the three patients who received only 15 mg/kg of body weight/day, two recovered completely and only minor residual changes were present in the third. The patient who received 25 mg/kg of body weight/day has a visual acuity of R.E.: 20/200 and L.E.: counting fingers. The author believes that other antituberculous drugs such as isoniazid and rifampin should be used whenever possible. (1 table, 15 references) —David Shoch

Graefe's Archive for Clinical and Experimental Ophthalmology

Treatment of retinal detachment with congenital optic pit by krypton laser photocoagulation. Annesley, W., Brown, G., Bolling, J., Goldberg, R., and Fisher, D. (Suite 135, Lankenau Med. Bldg., City Line & Lancaster Aves., Philadelphia, PA 19151). Graefes Arch. Clin. Exp. Ophthalmol. 225:311, 1987.

Five patients with congenital pits of the optic nerve and serous detachments of the macular retina were treated with juxtapapillary krypton laser photocoagulation. In four of the patients the subretinal fluid resolved and the macula reattached. The fifth patient required a pars plana vitrectomy to achieve a satisfactory result. One patient developed a macular hole and decreased visual acuity despite resolution of the subretinal fluid. (3 figures, 1 table, 10 references)—David Shoch

Nutritional amblyopia. Smiddy, W. E., and Green, W. R. (Eye Pathol. Lab., Johns Hopkins Hosp., 600 N. Wolfe St., Baltimore, MD 21205). Graefes Arch. Clin. Exp. Ophthalmol. 225:321, 1987.

Atrophy of the maculopapillary bundle was found on postmortem histologic examination of both eyes of 25 patients. A review of the medical records showed that 21 of the 25 patients had autopsies and good clinical histories were obtained on three additional patients. All 25 patients had nutritional deprivation, most commonly secondary to alcohol abuse. Of the eight patients who had advanced carcinoma, seven abused alcohol. Eleven patients smoked heavily. These histologic findings support the theory that tobacco-alcohol amblyopia is, in fact, nutritional amblyopia. (2 figures, 2 tables, 14 references)—David Shoch

Human Genetics

Detection of submicroscopic deletions and a DNA polymorphism at the retinoblastoma locus. Horsthemke, B., Greger, V., Barnert, H. J., Hopping, W., and Passarge, E. (Inst. fur Humangenetik and Zentrum fur Augenheilkunde, Universitatsklinikum, Hufelandstrasse 55, D-4300 Essen 1, West Germany). Hum. Genet. 76:257, 1987.

In a number of cases of bilateral or multifocal retinoblastoma, the retinoblastoma locus could be assigned to the long arm of chromosome 13, region 1, band 4. This locus is representative of a group of recessive oncogenes, and it is assumed that two genetic events are required to initiate tumor formation. In patients with familial retinoblastoma, the first event is a loss of function mutation at one of the two homologous retinoblastoma loci transmitted from the affected parent. Retinoblastoma develops in those patients who then have lost the normal retinoblastoma allele on the other chromosome either by chromosomal loss, mitotic crossing

over, gene conversion, deletion, or point mutation. This second somatic mutation often occurs in more than one retinoblast, resulting in bilateral multifocal unilateral retinoblastoma.

In about 60% of the patients, a retinoblastoma occurs because of two independent somatic mutations. This results in a nonhereditary retinoblastoma that is always unifocal and unilateral. The differences between the two types of retinoblastoma is not always clear, and a new probe, the anonymous DNA sequence H3-8, should help to differentiate between them. A significant proportion of germinal mutations at the retinoblastoma locus are caused by a deletion involving the H3-8 sequence. (2 figures, 1 table, 22 references) —David Shoch

Immunology

The role of autoimmune phenomena in the pathogenesis of cataract. Angunawela, I. I. (Dept. Pharmacol., Faculty of Med., Univ. Peradeniya, Peradeniya, Sri Lanka). Immunology 61:363, 1987.

The incidence of antilens protein antibodies was 44.4% in 45 healthy young adults who had no evidence of cataract or diabetes. In 50 patients with cataract, the incidence was 82%. In 50 patients with diabetes and no cataract, the incidence of antilens protein antibodies in the sera was 80%. In the four patients with both diabetes and cataract, all had antilens protein antibodies. The author postulates that in embryonic and early adult life, lens proteins are sequestered within a thick basement membrane. Proteins are released when this basement membrane thins and the body is unable to recognize the lens protein and produces antibodies. Patients who develop cataract may have positive antilens antibodies in their system for several years before cataract formation, thus accounting for their occurrence in healthy adults.

The author isolated an antigenic protein in the lens that had a molecular weight between 35,000 and 40,000. An antigen/antibody complex within the lens may result in loss of transparency and be a factor in cataract formation. Conversely, this may be a secondary phenomenon that is simply associated with cataract formation. (3 figures, 3 tables, 20 references) —David Shoch

Journal of the American Medical Association

Cutaneous myiasis of the eyelid due to *Cuterebra* larva. Cogen, M. S., Hays, S. J., and Dixon, J. M. (Dept. Ophthalmol., The Eye Found. Hosp., Univ. Alabama at Birmingham. Reprints not available). J.A.M.A. 258:1795, 1987.

A swollen, tender, nodule of the upper eyelid caused local redness and swelling that spread sequentially into the neck and face of a 28-year-old man. Despite the administration of several different antibiotics given both intramuscularly and intravenously, a periorbital cellulitis developed. The lesion was excised, and 48 hours later a cylindrical larva measuring 1.0 × 0.4 cm emerged at the incisional site. The larva was identified as a second-stage larva of the genus *Cuterebra*.

The patient had been bitten in the right clavicle region by an unidentified insect two weeks prior to his ocular symptoms. His initial complaint of a sensation of movement in the right upper eyelid was attributed to muscle contraction. Apparently the insect was a botfly, which deposited ova in the wound. The larva then developed and migrated to the skin of the eyelid. Myiasis should be considered in the differential diagnosis of furunculosis, particularly if conventional antibiotic therapy is unsuccessful. (2 figures, 12 references)—David Shoch

Journal of Neurology, Neurosurgery and Psychiatry

Ganzfeld electroretinographic findings in parkinsonism: untreated patients and the effect of levodopa intravenous infusion. Jaffe, M. J., Bruno, G., Campbell, G., Lavine, R. A., Karson, C. N., and Weinberger, D. R. (WAW, NIMH, 2700 Martin Luther King Ave., Washington, DC 20032). J. Neurol. Neurosurg. Psychiatry 50:847, 1987.

Electroretinograms were performed on seven patients with Parkinson's disease who had never received dopamimetic agents and six patients given an infusion of levodopa after a period of medication withdrawal. The patients who had never received dopamimetic drugs

showed a slight increase in the latency of their short-wavelength-sensitive cone response. In those patients who had received levodopa, the electroretinographic findings were significantly improved compared to baseline responses obtained during a period of medication withdrawal. These results suggest that dopamine is present in the retina, and that it may maintain the normal retinal responsiveness to flash stimuli. (3 figures, 3 tables, 22 references)—David Shoch

Adult onset supranuclear ophthalmoplegia, cerebellar ataxia, and neurogenic proximal muscle weakness in a brother and sister: another hexosaminidase A deficiency syndrome. Harding, A. E., Young, E. P., and Schon, F. (Dept. Clin. Neurol., Inst. Neurol., Queen Sq., London WC1N 3BG, England). J. Neurol. Neurosurg. Psychiatry 50:687, 1987.

A Jewish brother and sister with established hexosaminidase A deficiency developed supranuclear ophthalmoplegia, cerebellar ataxia, and neurogenic proximal muscle weakness in their fourth and fifth decades of life. Infantile Tay-Sachs disease is associated with a virtually undetectable activity of hexosaminidase A. The patients described here had hexosaminidase levels similar to that seen in infantile Tay-Sachs disease when the enzyme was assayed using a synthetic substitute. There is increasing evidence for marked clinical and molecular heterogeneity in the GM_2 gangliosidosis that warrants consideration of hexosaminidase A deficiency in the diagnosis of multisystem degenerative neurologic disorders, even with onset in adulthood. (1 figure, 2 tables, 12 references)—David Shoch

Journal of Rheumatology

Dose relationships in patients with early chloroquine retinopathy. Easterbrook, M. (170 St. George St., Suite 826, Toronto, Ontario, Canada M5R 2M8). J. Rheumatol. 14:472, 1987.

In 35 patients with bilateral irreversible chloroquine retinopathy, 30 were receiving a daily dose of 250 mg of chloroquine or less. The author recommends that the dosage of chloroquine be reduced as early as possible in patients with rheumatic disease. Visual field testing should be performed every six months or, preferably, the patient should examine his own central field with a grid device every two weeks. (1 table, 10 references)—David Shoch

Mechanisms of Ageing and Development

Lipofuscin autofluorescence: evidence for vitamin A involvement in the retina. Katz, M. L., Eldred, G. E., and Robison, W. G. (Mason Inst. Ophthalmol., Univ. Missouri School of Med., Columbia, MO 65212). Mech. Ageing Dev. 39:81, 1987.

Vitamin A deficiency in a strain of rats with inherited retinal dystrophy substantially reduced the autofluorescence associated with the degenerating photoreceptor cells. This in turn reduced the fluorophores in the retinal pigment epithelium. The authors concluded that the lipofuscin deposits in the retinal pigment epithelium are not primary to the cell but are the result of phagocytosis of the outer cell disks of the photoreceptors. (3 figures, 17 references)—David Shoch

Neurology

Acute "upside down" reversal of vision in transient vertebrobasilar ischemia. Steiner, I., Shahin, R., and Melamed, E. (Dept. Neurol., Hadassah Univ. Hosp., P. O. Box 12 000, Jerusalem 91 120, Israel). Neurology 37:1685, 1987.

On two occasions an 83-year-old man noted that everything appeared upside down. One time his bedside table and telephone appeared to hang down from the ceiling and on a second occasion the entire visual field was inverted with people hanging upside down from the ceiling. After the first episode he developed a transient right hemiparesis and hemihypesthesia, which resolved within ten minutes. During the second episode he experienced severe vertigo and nausea. Over the next two weeks the patient had transient episodes of right facial paresthesia and weakness of the right hand. This type of visual distortion has been reported in Wallenberg's syndrome (occlusion of the posterior inferior cerebellar ar-

tery) and appears to be a disorder of a central vestibulo-ocular integrative control mechanism. An anatomic location of the inversion described here is unknown. (7 references)—David Shoch

Obstetrical and Gynecological Survey

Maternal ocular adaptations during pregnancy. Weinreb, R. N., Lu, A., and Key, T. (Univ. California, San Diego, Dept. Ophthalmol., La Jolla, CA 92093). Obstet. Gynecol. Surv. 42:471, 1987.

Almost all ocular structures undergo some changes during pregnancy. The most serious change that can occur is probably a nonrhegmatogenous retinal detachment associated with marked hypertension and spasm of the retinal arterioles. The best treatment for the problem remains prompt delivery of the baby. Diabetic women are advised to have their babies early in life before the development of significant retinopathy and to have laser therapy of proliferative retinopathy before pregnancy. Conversely, it has been reported that patients with recurrent iritis tend to do better and intraocular pressure tends to drop during pregnancy. (4 figures, 3 tables, 141 references)—David Shoch

Transplantation

Human immunodeficiency virus transmission by organ donation. Schwarz, A., Hoffmann, F., L'age-Stehr, J., Tegzess, A. M., and Offermann, G. (Depts. Med. and Ophthalmol., Klinikum Steglitz, D-1000 Berlin 45, Germany). Transplantation 44:21, 1987.

The kidneys were removed from two donors, one of whom on retrospective testing for human immunodeficiency virus showed antibodies to the virus. The second donor had been a heroin addict for years but there was no record of serum studies for the immunodeficiency virus. One of the recipients of the kidney from the first donor died of severe pneumonia 16 days after kidney transplantation and no serum was available for study. The recipient of the second kidney from this first donor showed human immunodeficiency virus antibodies on day 50 and on all subsequent tests. The recipient of the right kidney of the second donor showed seroconversion on day 56 after transplantation. The second kidney of the second donor was not used. The corneas were also removed from the two donors and transplanted. Although there is currently no evidence of any transfer of the virus, in the late stages the human immunodeficiency virus is neurotropic and the antibodies may appear at a later date. All tissue and organ donors should be tested for antibodies to human immunodeficiency virus before donation. (1 figure, 1 table, 48 references)—David Shoch

NEWS ITEMS

Send News Items to
Editor
American Journal of Ophthalmology
Tribune Tower, Suite 1415
435 N. Michigan Avenue
Chicago, IL 60611

The Journal invites information concerning meetings, postgraduate courses, lectures, honors, and appointments. Double space each item and provide the name and address of the responsible author. Announcements of courses, meetings, and lectures must be submitted at least six months before the date of the event.

Second Annual African Ophthalmic Plastic and Reconstructive Surgery Symposium

The Second Annual African Ophthalmic Plastic and Reconstructive Surgery Symposium will be held March 7–12, 1988, in Mali, West Africa. For further information, write Stephen L. Bosniak, M.D., 300 Central Park West, New York, NY 10024.

European Glaucoma Society: Third Congress

The Third Congress of the European Glaucoma Society will be held in Esotril, Portugal, May 23–26, 1988. For further information, write Prof. Dr. E. L. Greve, Eye Clinic of the University of Amsterdam, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

International Society of Geographical Ophthalmology: Joint Meeting

The meeting of the International Society of Geographical Ophthalmology will be held jointly with the Ophthalmological Society of East Africa in Nairobi, Kenya, Aug. 3–5, 1988. For further information, write Prof. Gordon J. Johnson, Director, International Center for Eye Health, 27-29 Cayton St., London, EC1V 9EJ, England.

Allegheny General Hospital: Advanced Orbital Surgery: Techniques and Practical Experience

Allegheny General Hospital will sponsor a course, Advanced Orbital Surgery: Techniques and Practical Experience, April 16 and 17, 1988, in Pittsburgh, Pennsylvania. For further information, write Kathleen Hrdlicka, Continuing Medical Education, Allegheny General Hospital, 320 E. North Ave., Pittsburgh, PA 15212.

University of Bristol: Advanced Course in Ophthalmology

The University of Bristol will hold a full-time, one-year course, Advanced Course in Ophthalmology, beginning in October 1988. For further information, write Mrs. J. Galsworthy, Department of Ophthalmology, Bristol Eye Hospital, Lower Maudlin St., Bristol BS1 2LX England.

New York Society for Clinical Ophthalmology: Spring Meeting

The New York Society for Clinical Ophthalmology will hold its spring meeting, March 12, 1988, in New York, New York. For further information, write Francine Leinhardt, Course Coordinator, New York Society for Clinical Ophthalmology, 210 E. 64th St., New York, NY 10021.

College of Physicians and Surgeons of Columbia University: Continuing Education Programs

The College of Physicians and Surgeons of Columbia University will sponsor three continuing education programs: Clinical Laser Update, April 15, 1988; The Cutting Edge of Cataract Surgery: Most Effective Techniques and Latest Developments, April 16, 1988; and New and Proven Developments in Orbital and Ophthalmic Plastic Surgery, April 17, 1988. For further information, write College of Physicians & Surgeons of Columbia University, Continuing Education, 630 West 168th St., New York, NY 10032.

Doheny Eye Institute: Strabismus Surgery Techniques

The Doheny Eye Institute will hold a meeting, Strabismus Surgery Techniques, Feb. 6, 1988, in Los Angeles, California. For further information, write Laurie Woolf, Continuing Medical Education, Doheny Eye Institute, 1355 San Pablo St., Los Angeles, CA 90033.

University of Illinois: Clinical Challenges Day

The University of Illinois College of Medicine will hold a Clinical Challenges Day, March 9, 1988, in Chicago, Illinois. For further information, write University of Illinois at Chicago, Attn: Conference Registrar, Conferences and Institutes (M/C 607), 912 S. Wood St., Chicago, IL 60612.

Pacific Coast Oto-Ophthalmological Society: Annual Meeting

The Pacific Coast Oto-Ophthalmological Society will hold its annual meeting June 25–29, 1988, in Coronado, California. For further information, write Mireya A. Jones, PCOOS Manager, 1613 Chelsea Road, Suite 229, San Marino, CA 91108.

Pittsburgh Ophthalmology Society: 24th Annual Spring Meeting

The Pittsburgh Ophthalmology Society will hold its 24th Annual Spring Meeting, April 22 and 23, 1988, in Pittsburgh, Pennsylvania. For further information, write Pat Williamson, Registrar, The Pittsburgh Ophthalmology Society, 2545 Mosside Blvd., Monroeville, PA 15146.

Presbyterian Hospital of Dallas: Tenth Annual Dallas Spring Ophthalmology Symposium

The Presbyterian Hospital of Dallas will hold the Tenth Annual Dallas Spring Ophthalmology Symposium, March 25 and 26, 1988, in Dallas, Texas. For further information, write Lela Breckenridge, Office of Continuing Medical Education, Presbyterian Hospital of Dallas, 8200 Walnut Hill Lane, Dallas, TX 75231.

Eye Research Institute of Retina Foundation: 17th Annual Course in Practical Aspects of Photocoagulation

The Eye Research Institute of Retina Foundation will hold the Seventeenth Annual Course in Practical Aspects of Photocoagulation, April 7–9, 1988. For further information, write J. Wallace McMeel, M.D., Attn: Ms. J. Cerone, 100 Charles River Plaza, Boston, MA 02114.

New York Eye and Ear Infirmary: 24th Annual Survey Course

The New York Eye and Ear Infirmary will sponsor a course, Basic Subjects in Ophthalmology, March 7–12, 1988, in New York City. For further information, write Jane Stark, Registrar, Post Graduate Institute, New York Eye and Ear Infirmary, 310 E. Fourteenth St., New York, NY 10003.

Washington National Eye Center: Annual Symposium

The Washington National Eye Center and the Department of Ophthalmology of the Washington Hospital Center will sponsor its annual symposium, Advances in Glaucoma, April 22 and 23, 1988, in Washington, D.C. For further information, write the Washington National Eye Center, Suite 6B-13, 110 Irving St., N.W., Washington, D.C. 20010.

Wills Eye Hospital: 13th Annual Ophthalmology Review Course and 40th Annual Conference

Wills Eye Hospital will hold the 13th Annual Ophthalmology Review Course, March 12–16, 1988, in Philadelphia, Pennsylvania. For further information, write Lucia M. Manes, Wills Eye Hospital, Department of Continuing Medical Education, Ninth and Walnut Sts., Philadelphia, PA 19107.

Wills Eye Hospital will hold its 40th annual conference March 17–19, 1988, in Philadelphia, Pennsylvania. For further information, write Jeanne L. Kiska, Meeting Manger, 1621 Norristown Rd., Maple Glen, PA 19002.

Medical College of Wisconsin: Third Annual Eye Trauma Symposium

The Milwaukee Eye Institute will hold the Third Annual Trauma Symposium July 22 and 23, 1988, in Milwaukee, Wisconsin. For further information, write Prudie Helt, Eye Institute, Medical College of Wisconsin, 8700 W. Wisconsin Ave., Milwaukee, WI 53226.

Research to Prevent Blindness: Research Awards

Thaddeus P. Dryja has been named recipient of the $60,000 Research to Prevent Blindness Dolly Green Award to advance his studies in the molecular genetics of inherited eye diseases.

J. Bronwyn Bateman received the $45,000 William and Mary Greve International Award to advance her work in pediatric ophthalmology and the study of hereditary ocular diseases.

Paul Knepper received the $30,000 Olga Keith Wiess Award to assist his studies of complex carbohydrates present in the eye's trabecular meshwork.

Marguerite B. McDonald received the $25,000 James S. Adams Award for her pioneering work in corneal refractive surgery.

Basil V. Worgul received the $25,000 Robert E. McCormick Award to assist his studies of cellular changes in the cataractous lens resulting from environmental and other radiation.

$20,000 Manpower Awards were awarded to the following:

Einar Stefansson for his research in vitreoretinal diseases, with special focus on oxygen physiology as it relates to diabetic retinopathy.

Ran C. Zeimer who is using applied physics methods to develop noninvasive instrumentation for the measurement and study of biological processes in glaucoma and other problems of clinical ophthalmology.

Eric M. Lasater to assist his studies of information processing in the intact retina, using "white noise" analysis techniques.

Fight For Sight, Inc.: Scientific Awards 1987–1988

Mildred Weisenfeld, Executive Director of Fight For Sight, Inc., announced that 14 grants-in-aid, 13 postdoctoral research fellowships, continued support for four Fight For Sight Children's Eye Clinics, and two initial pediatric awards have been approved for 1987–1988 by the Fight For Sight Research Award Program, administered by the Association for Research in Vision and Ophthalmology.

Grants-in-Aid

Curtis R. Brandt, Ph.D., Dept. of Ophthalmology, University of Wisconsin (Madison, WI), "Viral factors involved in herpetic keratitis," $8,750.

Cheryl M. Craft, Ph.D., Dept. of Psychiatry, University of Texas (Dallas, TX), "Isolation of retinal cDNA for N-acetyltransferase," $9,000.

Peter J. Del Vecchio, Ph.D., Dept. of Ophthalmology, Albany Medical College (Albany, NY), "Sulfated polyanions in the control of ocular scarring," $8,750.

Lloyd N. Fleisher, Ph.D., Depts. of Anatomy, Physiological Sciences, and Radiology, North Carolina State University (Raleigh, NC), "Eicosanoid-glutathione interactions during ocular inflammation," $9,000.

Jeffrey S. Kay, M.D., Dept. of Ophthalmology, University of Arizona (Tucson, AZ), "Delivery of 5-FU and bleomycin in a collagen implant as adjuncts to glaucoma filtration surgery," $7,000.

Carl L. Keen, Ph.D., Depts. of Nutrition and Internal Medicine, University of California (Davis, CA), "Abnormal copper metabolism and macular degeneration" (In Honor of Bob Hope), $9,000.

Fred H. Lambrou, M.D., and Robert W. Snyder, M.D., Dept. of Ophthalmology, Medical College of Wisconsin (Milwaukee, WI), "Intraocular fibrinolysis using human tissue plasminogen activator," $6,400.

Mark A. Latina, M.D., Dept. of Ophthalmology, Harvard University (Boston, MA), "Selective photothermolysis of the ciliary body vasculature using pulsed transscleral irradiation to treat advanced glaucoma" (In Memory of Selma Rabin), $5,210.

Raga Malaty, M.D., Dept. of Ophthalmology, Louisiana State University (New Orleans, LA), "Neural-immune interactions in ocular inflammation," $9,000.

William M. Pierce, Jr., Ph.D., Dept. of Pharmacology and Toxicology, University of Louisville (Louisville, KY), "Topical carbonic anhydrase inhibitors," $9,000.

Hunson K. Soong, M.D., Dept. of Ophthalmology, University of Michigan (Ann Arbor, MI), "Effect of connective tissue activating peptide on corneal stromal wound healing," $9,000.

Dwight E. Stambolian, M.D., Dept. of Ophthalmology, University of Pennsylvania (Philadelphia, PA), "Genetic mapping of human X-linked eye diseases," $8,000.

Scheffer Tseng, M.D., and Andrew J. W. Huang, M.D., Dept. of Ophthalmology, University of Miami (Miami, FL), "Photothrombosis of corneal neovascularization by treatment with argon laser and intravenous rose bengal" $8,500.

Rosalyn E. Weller, Ph.D., Dept. of Psychology, University of Alabama (Birmingham, AL), "Renewed investigation of the transneuronal retrograde degeneration of ganglion cells of the retina" (In Memory of Silas Adelsheim), $9,000.

Postdoctoral Research Fellowships

Elias Aizenman, Ph.D., Dept. of Neurology, The Children's Hospital (Boston, MA) (Stuart A. Lipton, M.D., Sponsor), "Cholinergic modulation of process outgrowth in dissociated retinal ganglion cells," $12,000.

Dimitri T. Azar, M.D., Eye Research Institute (Boston, MA) (Ilene K. Gipson, Ph.D., Sponsor), "Corneal epithelial adhesion and wound healing in diabetes," $8,000.

Kuyas Bugra, Ph.D., Dept. of Anatomy, Mental Retardation Research Center (Los Angeles, CA) (James F. McGinnis, Ph.D., Sponsor), "Molecular characterization of the mouse

33 KD photoreceptor specific phosphoprotein," $9,000.

Cheryl A. Jackson, Ph.D., Dept. of Ophthalmology, University of Alabama (Birmingham, AL) (Cynthia Owsley, Ph.D., Sponsor), "Peripheral visual function in age-related macular degeneration," $12,000.

Randy H. Kardon, M.D., Dept. of Ophthalmology, University of Iowa (Iowa City, IA) (H. Stanley Thompson, M.D., Sponsor), "Objective pupil perimetry," $12,000.

Revathi Iyengar, Ph.D., Dept. of Ophthalmology, Columbia University (New York, NY) (Abraham Spector, Ph.D., Sponsor), "Synthesis of synthetic GSH peroxidase and its utilization to prevent maturity onset cataract" (In Honor of Charles A. Perera, M.D.), $12,000.

Hilel Lewis, M.D., Dept. of Ophthalmology, Johns Hopkins University (Baltimore, MD) (Stuart L. Fine, M.D., Sponsor), "Peripheral retinal function in patients with multiple extramacular drusen and patients with reticular dystrophy of the retinal pigment epithelium," $12,000.

Bih-Hwa Shieh, Ph.D., Dept. of Biology, University of California, San Diego (La Jolla, CA) (Dr. Charles Zuker, Sponsor), "The molecular basis of the spectral specificity of rhodopsins," $12,000.

Bryan S. Sires, Ph.D., Dept. of Ophthalmology, Northwestern University (Chicago, IL) (Paul A. Knepper, M.D., Sponsor), "The extracellular matrix of the trabecular meshwork and growth factors and their relationship to primary open angle glaucoma," $3,000.

William R. Taylor, Ph.D., Depts. of Ophthalmology and Physiology, University of California (San Francisco, CA) (David R. Copenhagen, Ph.D., Sponsor), "Patch-clamp analysis of the excitatory inputs to ganglion cells in the vertebrate retina," $10,500.

Rohit Varma, M.D., Wills Eye Hospital (Philadelphia, PA) (George L. Spaeth, M.D., Sponsor), "Optic disc analysis," $12,000.

Akio Yokota, M.D., Dept. of Ophthalmology, University of Michigan (Ann Arbor, MI) (Prof. Mathew Alpern, Sponsor), "Classical tritanopia associated incipient with diabetic retinopathy" (In Memory of Mrs. Charles A. Perera, "Ruth"), $12,000.

Motohiro Kiyosawa, M.D., Neuro-Ophthalmology Unit, Wills Eye Hospital (Philadelphia, PA) (Peter J. Savino, M.D., Sponsor), "Positron emission tomography and vision" (Special Award funded by Fight For Sight of Greater Philadelphia), $12,000.

Service Projects

The Board of Directors of the organization approved renewal support in relatively modest amounts to four Fight For Sight Children's Eye Clinics and two additional Pediatric Awards:

Columbia-Presbyterian Medical Center, New York City, Howard M. Eggers, M.D., Director, $3,000.

Eye Institute of New Jersey, Newark, Anthony R. Caputo, M.D., Director, $7,045.

Children's Hospital of the University of Pittsburgh, David Hiles, M.D., Director, $3,500.

Wills Eye Hospital, Philadelphia, Joseph Calhoun, M.D., Director, $14,048.

Children's Hospital of Philadelphia, David B. Schaffer, M.D., Specialized instruments for use in the examination of infants and children while under anesthesia (funded by a grant from the Fight For Sight of Greater Philadelphia), $14,300.

The Pediatric Ophthalmic Oncology Center, New York Hospital-Cornell Medical Center, Robert Ellsworth, M.D., Director, for the purchase of a ceiling-mounted fundus camera, $25,000.

Nominations for Von Sallmann Prize

The Ludwig Von Sallmann Prize will be awarded at the 8th International Congress of Eye Research to be held from Sept. 4–8, 1988, in San Francisco, California. For further information, write Peter Gouras, M.D., Von Sallmann Prize Committee, Columbia University, Box 18, 630 West 168th St., New York, NY 10032.

Lowe's Syndrome Association: Research Proposals

The Lowe's Syndrome Association, Inc., requests research proposals aimed at achieving a better understanding of the cause of Lowe's syndrome and/or developing better treatments for the major complications. Grant award up to $5,000. The application deadline is June 1, 1988. For further information, write Lowe's Syndrome Association, Inc., 222 Lincoln St., West Lafayette, IN 47906.

RP Foundation Fighting Blindness: Research Support

The RP Foundation Fighting Blindness plans to take part in the establishment of one or more additional centers for the study of retinitis pigmentosa, Usher's syndrome, macular degeneration and allied hereditary retinal degen-

eration. To that end, the Foundation invites center grant proposals for research support. Center programs should be directed toward an understanding of the cause of one or more types of retinal degeneration by means of basic studies in the anatomy, physiology, biochemistry, molecular biology and genetics of the retina, especially as concerns photoreceptors and pigment epithelial cells. The deadline for submission of proposals is March 1, 1988. For further information, write Jeanette S. Felix, Ph.D., Director of Science, RP Foundation Fighting Blindness, 1401 Mt. Royal Ave., Baltimore, MD 21217.

Merck & Co., Inc.: Free Onchoceriasis Drug

Merck and Co., Inc., will provide its antiparasitic drug, Mectizan, free of charge to countries that need it to eradicate onchocerciasis that affects as many as 20 million people in Africa, South and Central America, and the Middle East. About 340,000 people are blinded by the disease. Mectizan is effective in small doses given only one or twice a year and has few side effects. The World Health Organization will distribute the drug and supervise the medical care. The disease may be eradicated by the end of the century.

Personals

Stephen Drance

Stephen Drance was appointed to the Order of Canada. Dr. Drance was honored for his contributions to Canadian society.

Herbert E. Kaufman

Herbert E. Kaufman was awarded the Castroviejo Medal at the 1987 annual meeting of the American Academy of Ophthalmology, Nov. 10, 1987, in Dallas, Texas.

Paul R. Lichter

Paul R. Lichter will give the 33rd Annual Albert C. Snell Memorial Lecture at the Annual Ophthalmology Conference of the Rochester Ophthalmologic Society March 25 and 26, 1988, in Rochester, New York.

Homer Smith

Homer Smith, of Salt Lake City, Utah, was elected first vice-president of the American College of Surgeons at their annual meeting. He has been a member of the Board of Regents of the College.

Stanley M. Truhlsen

Stanley M. Truhlsen, Omaha, Nebraska, has been named chairman of the Ophthalmic Advisory Committee of the American College of Surgeons.

George W. Weinstein

George W. Weinstein, Morgantown, West Virginia, has been named to the Board of Regents of the American College of Surgeons.

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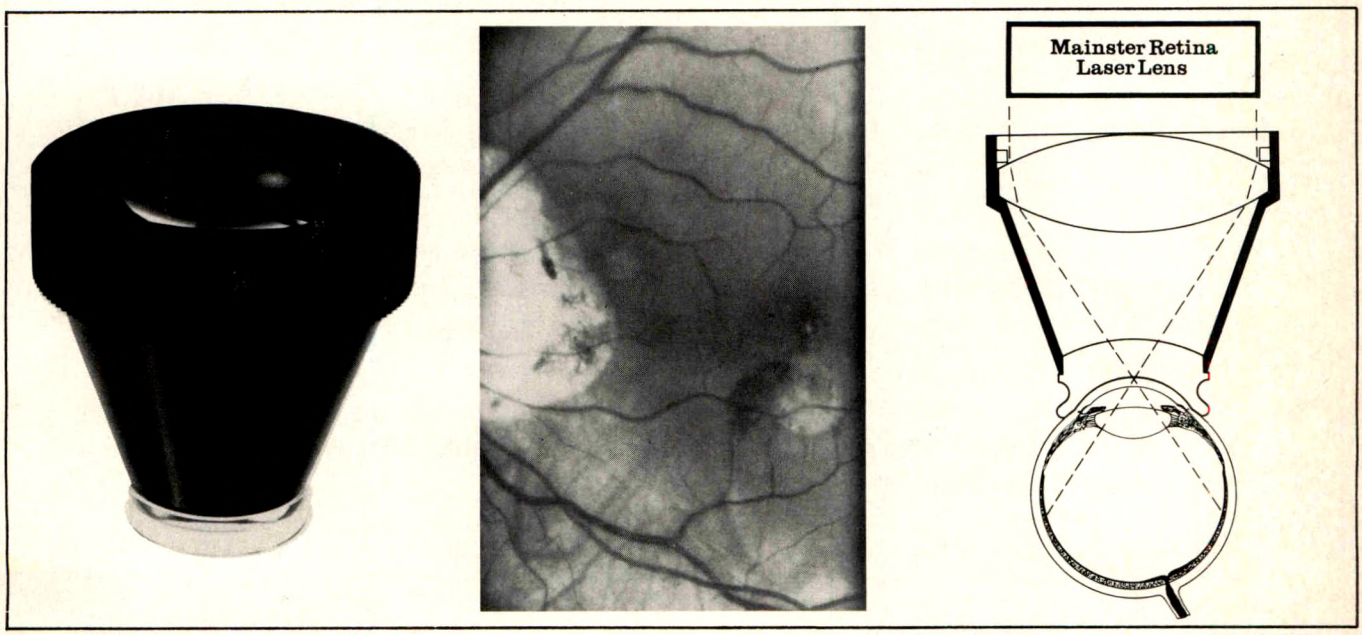


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Tuition is $1400. For further information and application forms, please write to **J. W. Bettman, M.D., Department of Ophthalmology, A-157, Stanford Medical Center, Stanford, California 94305.**

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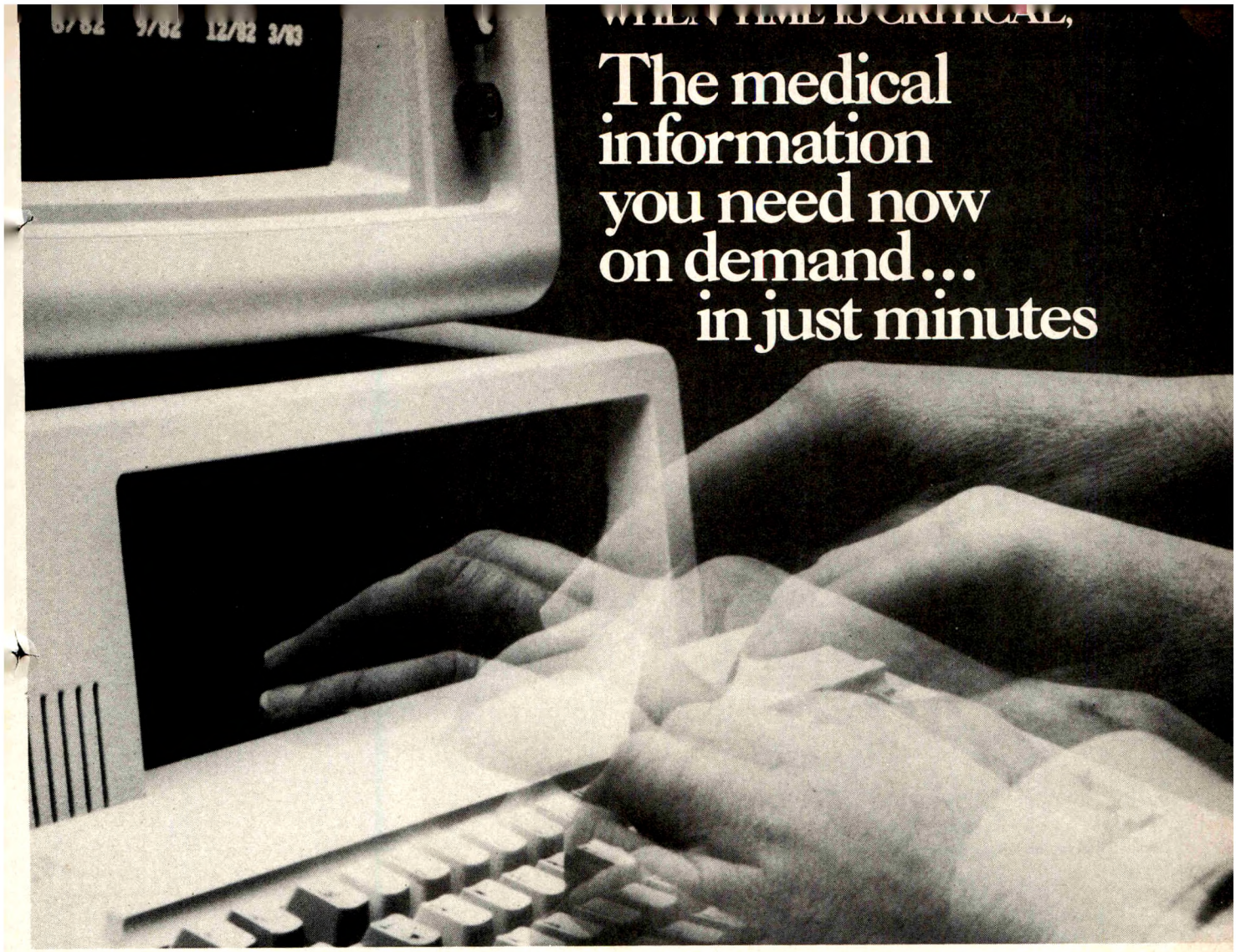
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Guest speakers from Puerto Rico:

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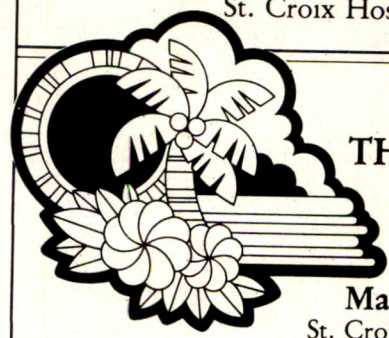
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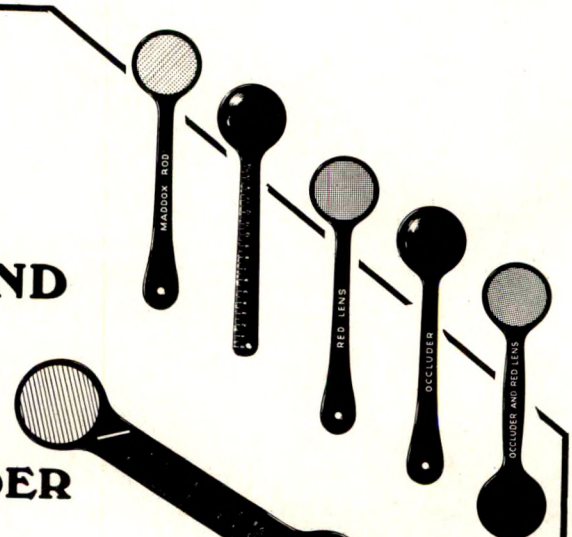
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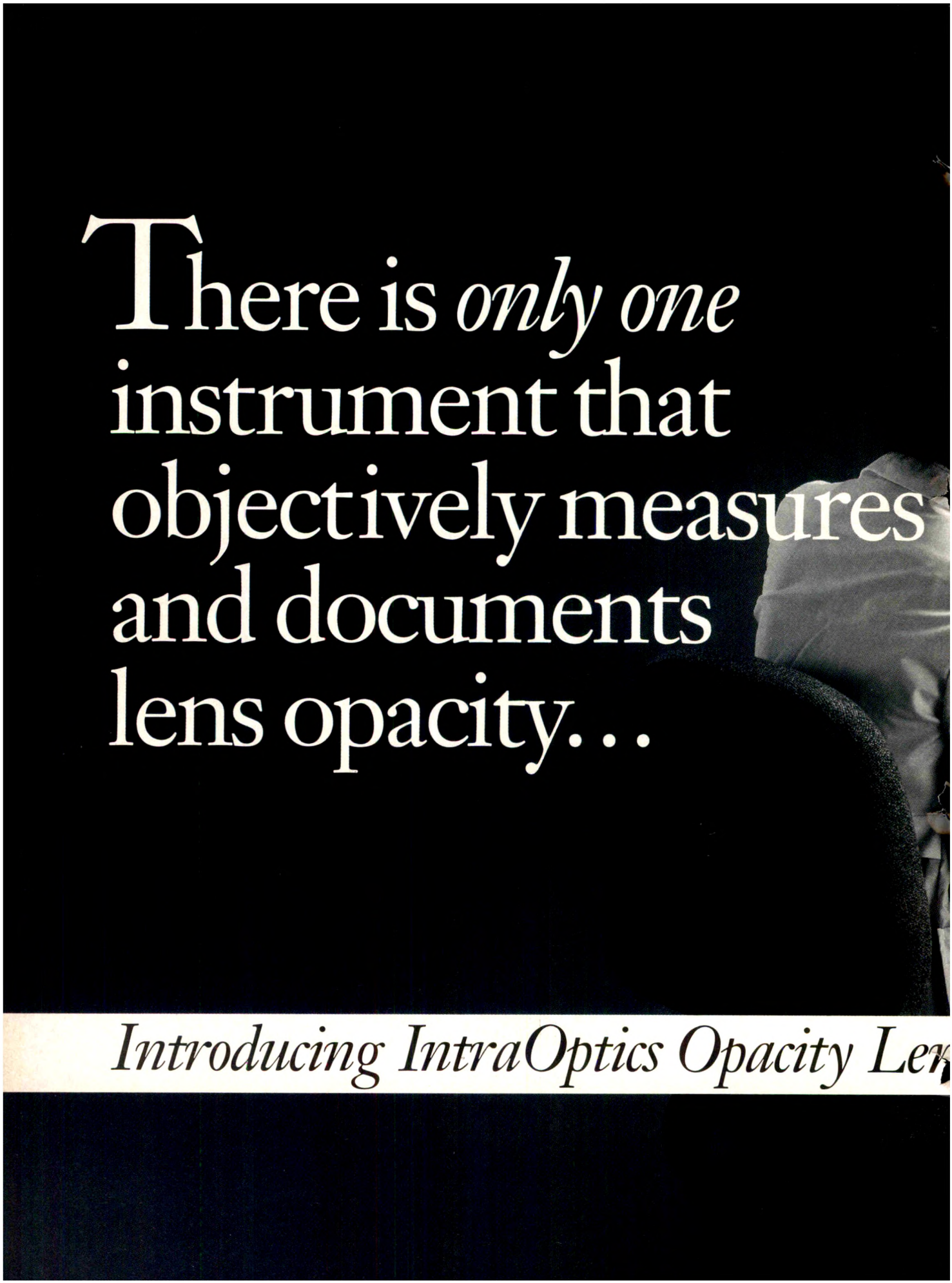
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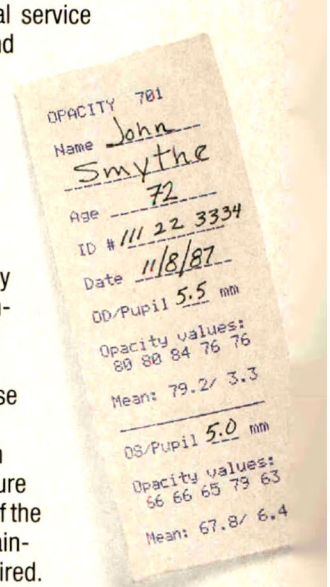


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J. R. Kerstetter, M.S., R. F. Brubaker, M.D, S. E. Wilson, M.D., and L. J. Kullerstrand, B.S.

Using fluorophotometry, we performed a randomized, dose-response study of the effects of a prostaglandin derivative on aqueous humor flow. Prostaglandin $F_{2\alpha}$-1-isopropylester, 0.224 μg, 0.448 μg, and 1.120 μg, in saline with polysorbate 80 was instilled into one eye of 20 subjects in three separate dose studies. Polysorbate 80 in saline was instilled in the fellow eye as a control. The drug had no measurable effect on aqueous humor flow or corneal endothelial permeability. Intraocular pressure measured eight hours after administration of the highest dose, 1.120 μg, was 20% lower in the treated eye as compared to the fellow eye ($P < .001$).

© American Journal of Ophthalmology 105:30–34, January, 1988

Response of Blood Flow to Warm and Cold in Normal and Low-Tension Glaucoma Patients

S. M. Drance, M.D., G. R. Douglas, M.D., K. Wijsman, M. Schulzer, Ph.D., and R. J. Britton, M.D.

We measured blood flow in the finger in 38 control subjects with normal ocular findings without migraine, 13 control subjects with normal ocular findings with classic migraine, 17 patients with low-tension glaucoma with classic migraine, and 29 patients with low-tension glaucoma without migraine. Three blood flow measurements were recorded: one at baseline, one after immersion in warm water (40 C), and one after ten seconds' exposure to cold water (4 C). The mean baseline flow and the mean flow after exposure to cold were lower in patients with low-tension glaucoma ($P = .013$ and $P < .001$, respectively).

© American Journal of Ophthalmology 105:35–39, January, 1988

The Lenz Microphthalmia Syndrome

Elias I. Traboulsi, M.D., Widukind Lenz, M.D., Mario Gonzales-Ramos, M.D., Jacqueline Siegel, M.D., William G. Macrae, M.D., and Irene H. Maumenee, M.D.

We examined two patients with the Lenz microphthalmia syndrome. When findings from these two patients and those from ten other patients in the literature were combined, the following abnormalities were observed: microphthalmos in all patients; developmental retardation in 11 patients (92%); external ear abnormalities in ten patients (83%); microcephaly in ten patients (83%); blepharoptosis in nine patients (75%); skeletal anomalies (excluding digital anomalies) in eight patients (67%); dental abnormalities of number and position in eight patients (67%); digital anomalies in seven patients (58%); urogenital anomalies in six patients (50%); and cleft lip and palate abnormalities in four patients (33%). Cardiac anomalies, imperforate anus, hearing loss, spastic diplegia, sacral pits, webbed neck, and abnormal dermatoglyphs were rarely seen. One of our two patients had a dislocated lens and retinal detachment.

© American Journal of Ophthalmology 105:40–45, January, 1988

Cosegregation of X-Linked Retinitis Pigmentosa and Hemophilia A

Yaron S. Rabinowitz, M.D., Roger L. Ladda, M.D., Joseph W. Sassani, M.D., and M. Elaine Eyster, M.D.

We examined a family pedigree in which retinitis pigmentosa and hemophilia A were inherited in an X-linked manner. Six female carriers were identified by electroretinography. Results of ophthalmoscopic examination were normal in two women, while four displayed marked variability in phenotypic expression. Six of seven males identified with retinitis pigmentosa had hemophilia A. One asymptomatic boy had a markedly abnormal electroretinogram despite normal ophthalmoscopic examination. Pedigree analysis showed a high recombination rate, which would be expected as these two genes are known to be at opposite arms of the X chromosome.

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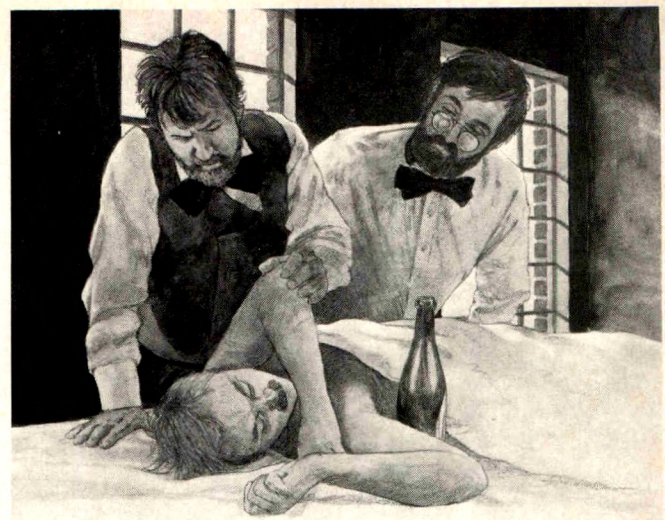
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The Surgical Treatment of Blepharoptosis in Oculomotor Nerve Palsy

Timothy J. Malone, M.D., and Jeffrey A. Nerad, M.D.

We reviewed retrospectively 170 cases of congenital and acquired oculomotor nerve palsy to determine the effectiveness of surgery in the treatment of blepharoptosis in oculomotor nerve palsy. Twenty patients had had surgical repair of the blepharoptosis. Patients with congenital oculomotor palsy were more often selected for blepharoptosis surgery than patients with acquired blepharoptosis because of the absence of diplopia caused by suppression in congenital cases. There was complete recovery in 72 of 109 patients (66%) with acquired oculomotor palsy. Results were judged with regard to functional improvement and cosmetic improvement. Primary functional disability was relieved by lifting the eyelid above the pupil in ten of 12 patients (83%). Primary cosmetic disability was relieved in six of six patients. Corneal complications occurred in six of 20 patients (30%) who were treated surgically.

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Linear Subcutaneous Fat Atrophy After Corticosteroid Injection of Periocular Hemangiomas

Patrick J. Droste, M.D., Forrest D. Ellis, M.D., Naval Sondhi, M.D., and Eugene M. Helveston, M.D.

Two children developed evidence of subcutaneous fat atrophy after corticosteroid injection of periocular hemangiomas. The atrophy appeared at the site of injection and followed the expected course of lymphatic channels to the vicinity of regional lymph nodes.

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Postkeratoplasty Crystalline Deposits Mimicking Bacterial Infectious Crystalline Keratopathy

Robert W. Weisenthal, M.D., Jay H. Krachmer, M.D., Robert Folberg, M.D., Steven P. Dunn, M.D., and William E. Whitson, M.D.

Three corneal transplant patients developed white, crystalline, anterior stromal lesions in their grafts while receiving long-term topical corticosteroid therapy. A presumed diagnosis of infectious crystalline keratopathy was made in each case. However, histologic examination of the lesions failed to show gram-positive cocci. A fungal infiltrate was present in the first two patients, and calcium deposits produced the lesion in the third patient.

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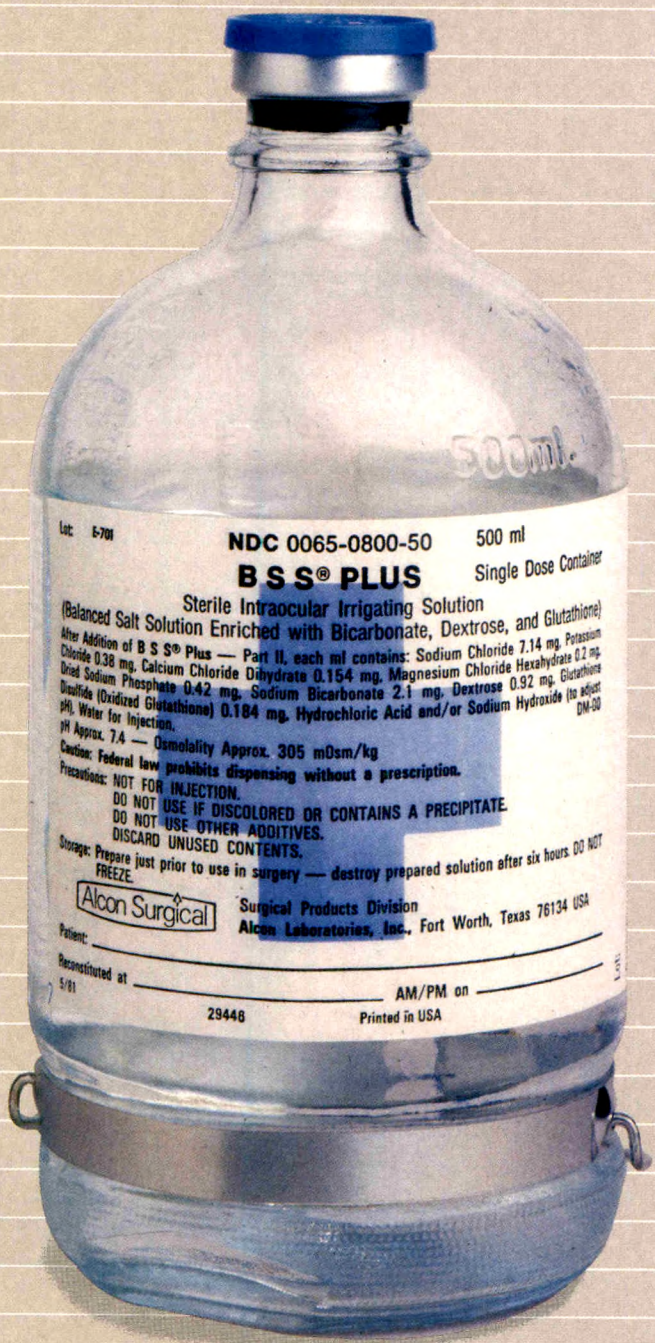
Bilateral Keratitis as a Manifestation of Lyme Disease

Jules Baum, M.D., Michael Barza, M.D., Philip Weinstein, M.D., Joseph Groden, M.D., and Milhim Aswad, M.D.

An 11-year-old girl developed bilateral keratitis, which we believe was a manifestation of Lyme disease. She had had several attacks of Lyme arthritis and was twice treated with parenteral penicillin. The keratitis developed five years after the initial episode of Lyme arthritis at a time when there were no other manifestations of Lyme disease. It cleared completely in both eyes after topical corticosteroid therapy.

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The solution does not contain a preservative and should be prepared just prior to use in surgery.

Part I: A sterile 28.8 mL solution in a 30 mL single-dose plastic bottle or a sterile 480 mL solution in a 500 mL single-dose bottle to which the Part II concentrate is added. Each mL of Part I contains: Sodium Chloride 7.44 mg, Potassium Chloride 0.395 mg, Anhydrous Dibasic Sodium Phosphate 0.433 mg, Sodium Bicarbonate 2.19 mg, Hydrochloric Acid and/or Sodium Hydroxide (to adjust pH), in Water for Injection. DM-00

Part II: 30 mL size: A sterile concentrate in a 1.2 mL single-dose syringe for addition to Part I. 500 mL size: A sterile concentrate in a 20 mL single-dose vial for addition to Part I. Each mL of Part II contains: Calcium Chloride Dihydrate 3.85 mg, Magnesium Chloride Hexahydrate 5 mg, Dextrose 23 mg, Glutathione Disulfide (Oxidized Glutathione) 4.6 mg, in Water for Injection. DM-00

After addition of BSS PLUS® Part II to the Part I bottle, each mL of reconstituted product contains: Sodium Chloride 7.14 mg, Potassium Chloride 0.38 mg, Calcium Chloride Dihydrate 0.154 mg, Magnesium Chloride Hexahydrate 0.2 mg, Anhydrous Dibasic Sodium Phosphate 0.42 mg, Sodium Bicarbonate 2.1 mg, Dextrose 0.92 mg, Glutathione Disulfide (Oxidized Glutathione) 0.184 mg, Hydrochloric Acid and/or Sodium Hydroxide (to adjust pH), in Water for Injection.

The reconstituted product has a pH of approximately 7.4. Osmolality is approximately 305 mOsm/kg.

CONTRAINDICATIONS: There are no specific contraindications to the use of BSS PLUS,® however, contraindications for the surgical procedure during which BSS PLUS® is to be used should be strictly adhered to.

WARNINGS: For IRRIGATION during ophthalmic surgery only. BSS PLUS® is NOT for injection or intravenous infusion.

PRECAUTIONS: DO NOT USE BSS PLUS® UNTIL RECONSTITUTED. Do not use Part I if it does not contain a vacuum (500 mL size). Do not use additives other than Part II. Do not use if Part I, Part II or the reconstituted solution is discolored or contains a precipitate. SINCE BSS PLUS IS INTENDED FOR INTRAOCULAR IRRIGATION, IT DOES NOT CONTAIN A PRESERVATIVE AND, THEREFORE, SHOULD NOT BE USED ON MORE THAN ONE PATIENT. DISCARD ANY UNUSED SOLUTION SIX HOURS AFTER PREPARATION. Studies suggest that intraocular irrigating solutions which are iso-osmotic with normal aqueous fluids should be used with caution in diabetic patients undergoing vitrectomy since intraoperative lens changes have been observed.

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3. O'Connor, G. R.: Herpes zoster uveitis. In Kraus-Mackiw, E., and O'Connor, G. R. (eds.): Uveitis. Pathophysiology and Therapy. New York, Thieme-Stratton, 1983, pp. 56–65.

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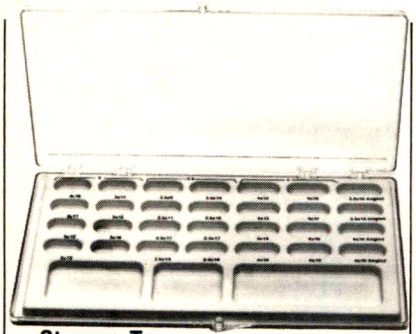
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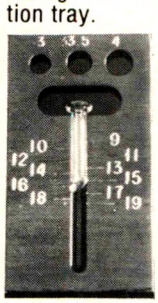
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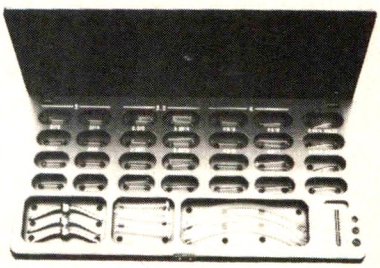
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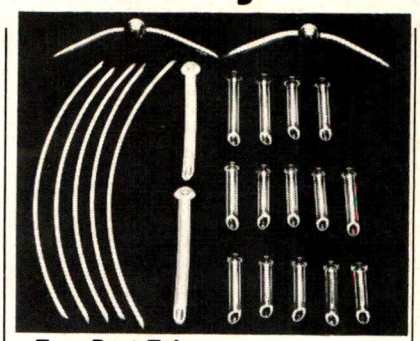
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*L.T. Jones M.D., Dacryocystorhinostomy, American Journal of Ophthalmology, Volume 59, No. 5, May, 1965.
J.C. Mustarde', L.T. Jones M.D. and A. Callahan M.D., Ophthalmic Plastic Surgery---Up-To-Date, Aesculapius Publishing Company, 1970.
L.T. Jones M.D. and J.L. Wobig M.D., Surgery of the Eyelids and Lacrimal System, Aesculapius Publishing Company, 1976.

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Send CV with references and correspondence to **Chief Executive Officer, Carle Clinic Association, Urbana, IL 61801.** Inquiries will be kept confidential.

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PEDIATRIC OPHTHALMOLOGIST

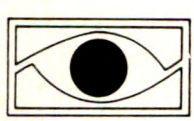
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Ophthalmologist with subspecialty training in Pediatric Ophthalmology is sought for full time position in University Department of Ophthalmology; a background or interests in genetics is desirable. Academic rank commensurate with credentials. Must have completed an approved eye residency training program, appropriate fellowship training, and be Board certified or eligible. Duties include teaching residents and medical students, patient care and research. Send curriculum vitae, publications list and the names and addresses of 3 references to:

James P. McCulley, M.D.
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Decreased Expression of HLA Class II Antigens on Human Uveal Melanoma Cells After In Vivo X-ray Irradiation

Martine J. Jager, M.D., Jeroen P. van der Pol, M.D., Didi de Wolff-Rouendaal, M.D., Paul T. V. M. de Jong, M.D., and Dirk J. Ruiter, M.D.

In order to determine the presence of HLA antigens on human uveal melanomas, we tested anti-HLA monoclonal antibodies on tissue sections of these tumors. A great variety in expression of HLA class I and II antigens was present. A significantly lower expression of HLA class II antigens was present on uveal melanomas that had been irradiated before enucleation. These tumors lacked a lymphocytic infiltrate in comparison with nonirradiated tumors. These data suggest that radiotherapy affects expression of histocompatibility antigens on tumors.

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Pacific Coast Oto-Ophthalmological Society (PCOOS)

ANNUAL MEETING

June 25 - June 29, 1988
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Coronado, California

Guest Speakers for Ophthalmology:

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Wills Eye Hospital
Philadelphia, Pennsylvania

Theodore Krupin, M.D.
Scheie Eye Institute
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Papers requested on any ophthalmology subject. Send abstracts by March 1, 1988 to Alan S. Crandall, M.D., Department of Ophthalmology, 50 N. Medical Drive, Salt Lake City, UT 84132.

PCOOS Ophthalmology Resident Award of $500 for outstanding paper with a resident as the principal author. To qualify for this award, an abstract must be submitted for the program by March 1 and a complete manuscript must be sent to Dr. Crandall by April 15, 1988.

For information regarding the meeting, contact:
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1613 Chelsea Road, Suite 229
San Marino, CA 91108
Phone: (818) 799-8610

GLAUCOMA

Ophthalmologist with subspecialty training in glaucoma is sought for full-time position in University Department of Ophthalmology, academic rank commensurate with credentials. Must have completed an approved eye residency program, appropriate fellowship training and be Board certified or eligible. Duties include teaching residents and medical students, patient care and research. Send curriculum vitae, publications list and the names and addresses of 3 references to:

James P. McCulley, M.D.
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Full-time faculty position for an individual with subspecialty training in glaucoma and an ability to be licensed in Texas. The physician must be able to develop and direct an academic service. Candidate must have also completed an accredited residency program, and be board certified or eligible in ophthalmolgy. Salary and benefits commensurate with training and experience. Please forward your curriculum vitae and the names of four references to:

James Price, M.D., Ph.D.
Professor and Chairman
Department of Ophthalmology & Visual Sciences
Texas Tech University Health Sciences Center
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Ophthalmologist with subspecialty training in glaucoma and interest in laboratory research is sought for a full-time position in the Department of Ophthalmology. Academic rank commensurate with credentials. Qualifications include completion of an approved residency program, fellowship training and Board certification. Duties include patient care, research, teaching residents and medical students. Send curriculum vitae, publication list, and references to:

Robert Machemer, M.D.
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James Price, M.D., Ph.D.
Professor and Chairman
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ANESTHESIOLOGIST: Board Certified, 33, American Medical Graduate, desires practice with Ophthalmology group in the Northwest Washington State area. Performs regional, local, or general anesthesia. Send inquiries to Box 003 AJO.

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Viral, bacterial and fungal infections of the cornea may be exacerbated by the application of steroids. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with the use of topical steroids. Acute purulent untreated infection of the eye may be masked or activity enhanced by the presence of steroid medication. • These drugs are not effective in mustard gas keratitis and Sjogren's keratoconjunctivitis. • If irritation persists or develops, the patient should be advised to discontinue use and consult prescribing physician. ■ **PRECAUTIONS:** As fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid applications, fungus invasion must be suspected in any persistent corneal ulceration where a steroid has been used or is in use. • Intraocular pressure should be checked frequently. • These products are sterile when packaged. To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or any other surface with the dropper tip of the bottle. Keep out of the reach of children. Keep bottle tightly closed. Protect from light. STORE AT CONTROLLED ROOM TEMPERATURE (15°-30°C) (59°-86°F). • **Pregnancy: Teratogenic Effects: Pregnancy Category C:** Animal reproductive studies have not been conducted with prednisolone sodium phosphate. It is also not known whether prednisolone sodium phosphate can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Prednisolone sodium phosphate should be given to a pregnant woman only if clearly needed. • The effect of prednisolone sodium phosphate on the later growth, development and functional maturation of the child is unknown. • **Nursing Mothers:** It is not known whether this drug is excreted in human milk. 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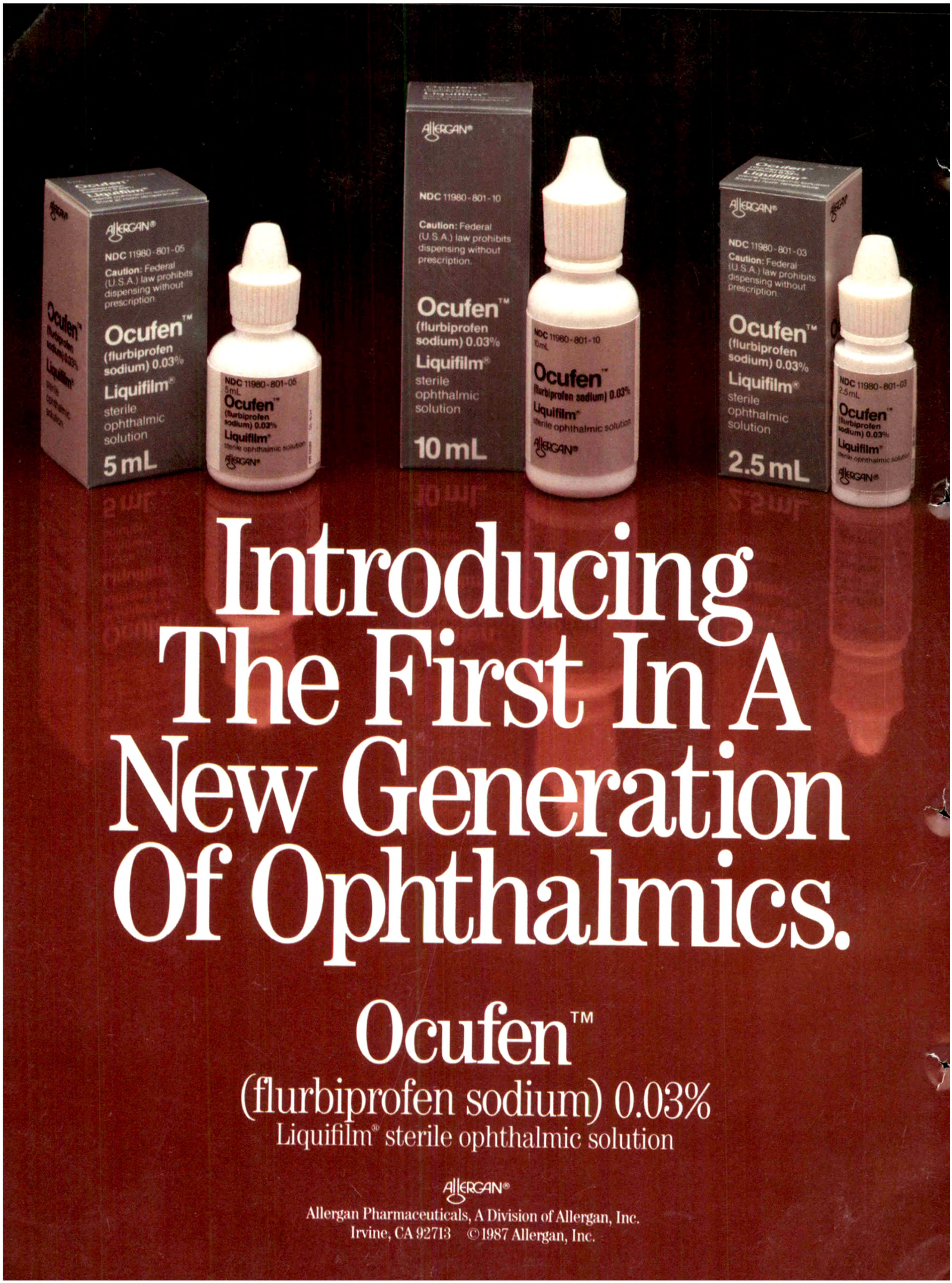
[1] *Kupferman, A., Ph.D., and Leibowitz, H.M., M.D. Topically applied steroids in corneal disease. Arch Ophthalmol: 92;1974, 331-334.*

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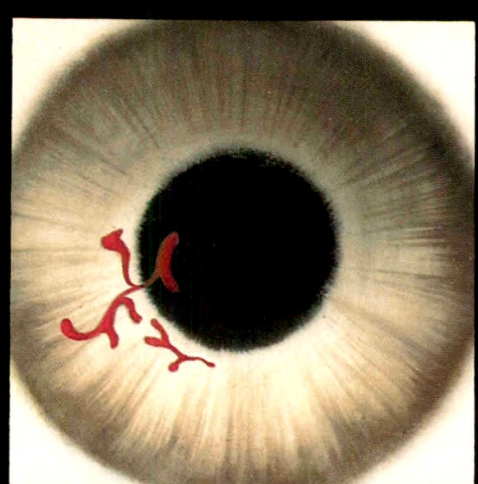
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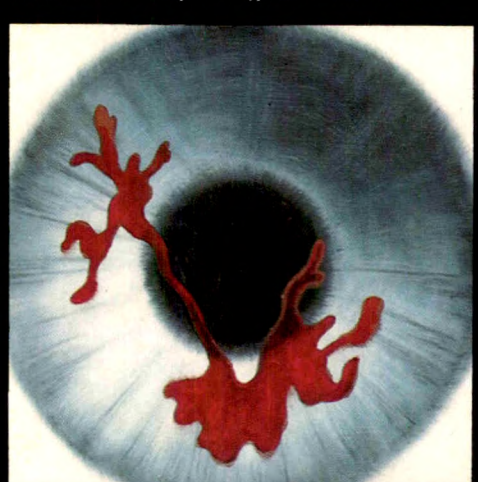
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(Medical artist's conception of typical Dendritic Lesion)

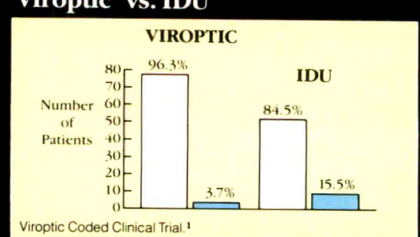
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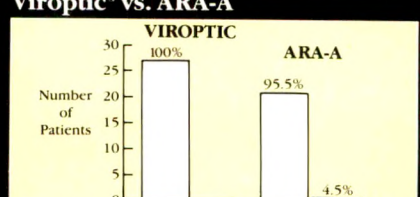
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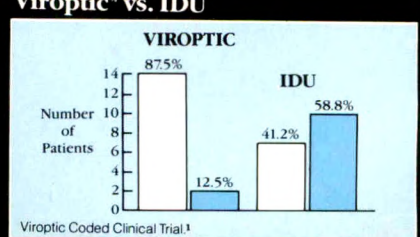
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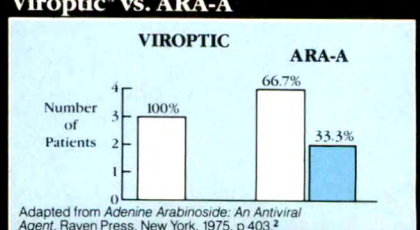
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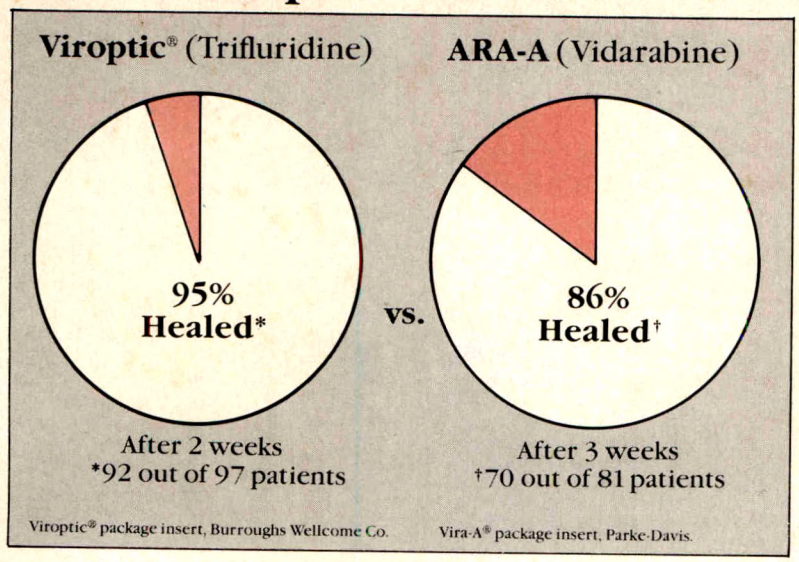
Number of Patients Healed

Number of Patients Not Healed

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References

1. Data on file, Medical Division, Burroughs Wellcome Co.
2. McKinnon JR, McGill JI, Jones BR: A coded clinical evaluation of adenine arabinoside and trifluorothymidine in the treatment of ulcerative herpetic keratitis, in Pavan-Langston D, Buchanan RA, Alford CA Jr (eds): *Adenine Arabinoside: An Antiviral Agent,* Raven Press, New York, 1975, p 403.
3. Kaufman HE, Centifanto-Fitzgerald YM, Varnell ED: Herpes simplex keratitis. *Ophthalmology* 1983;90:700-706.

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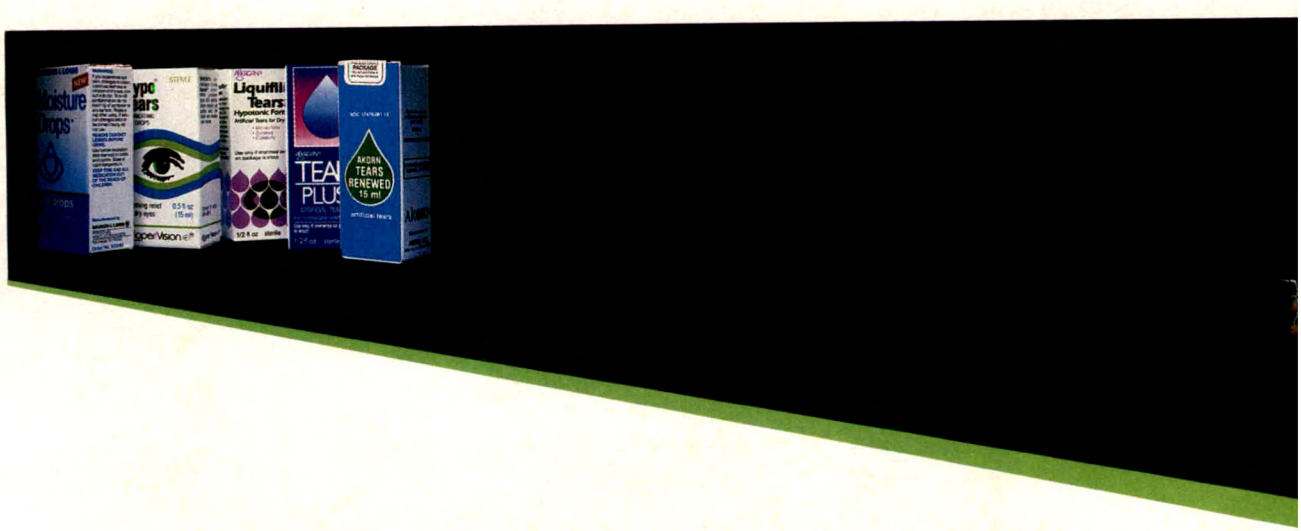
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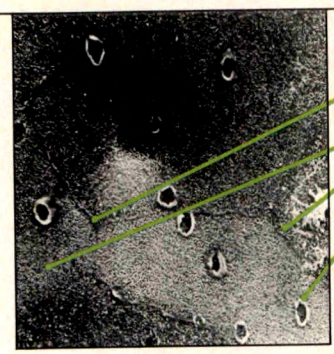


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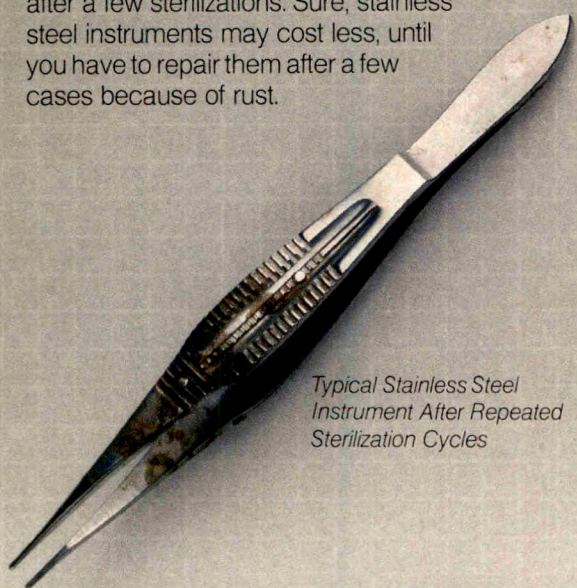
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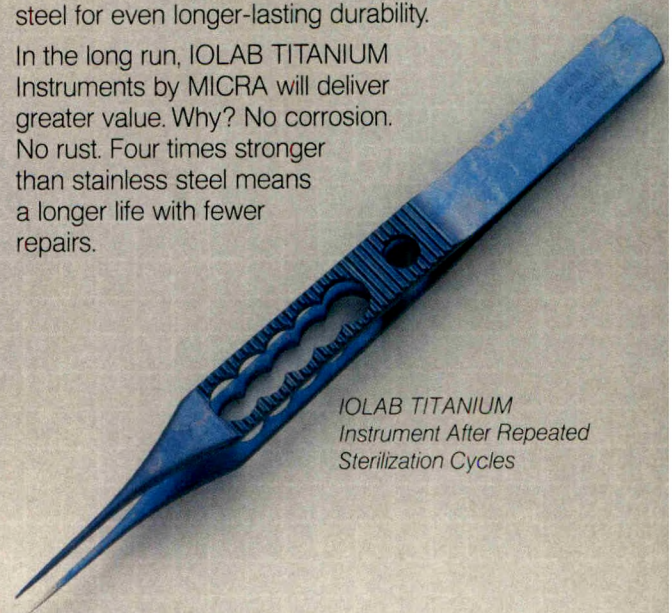


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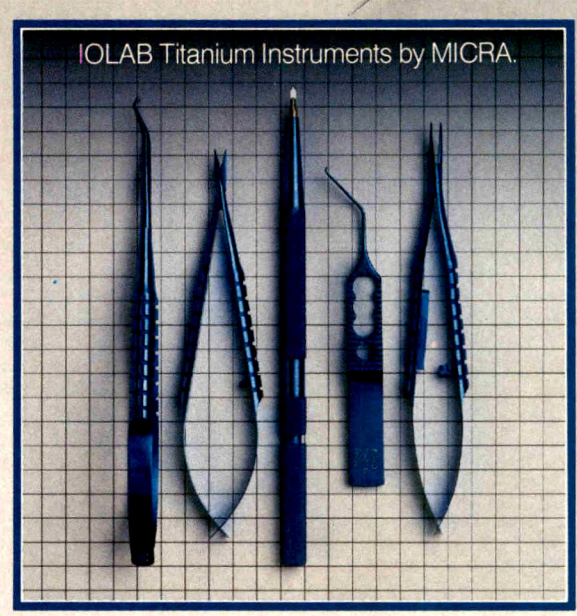
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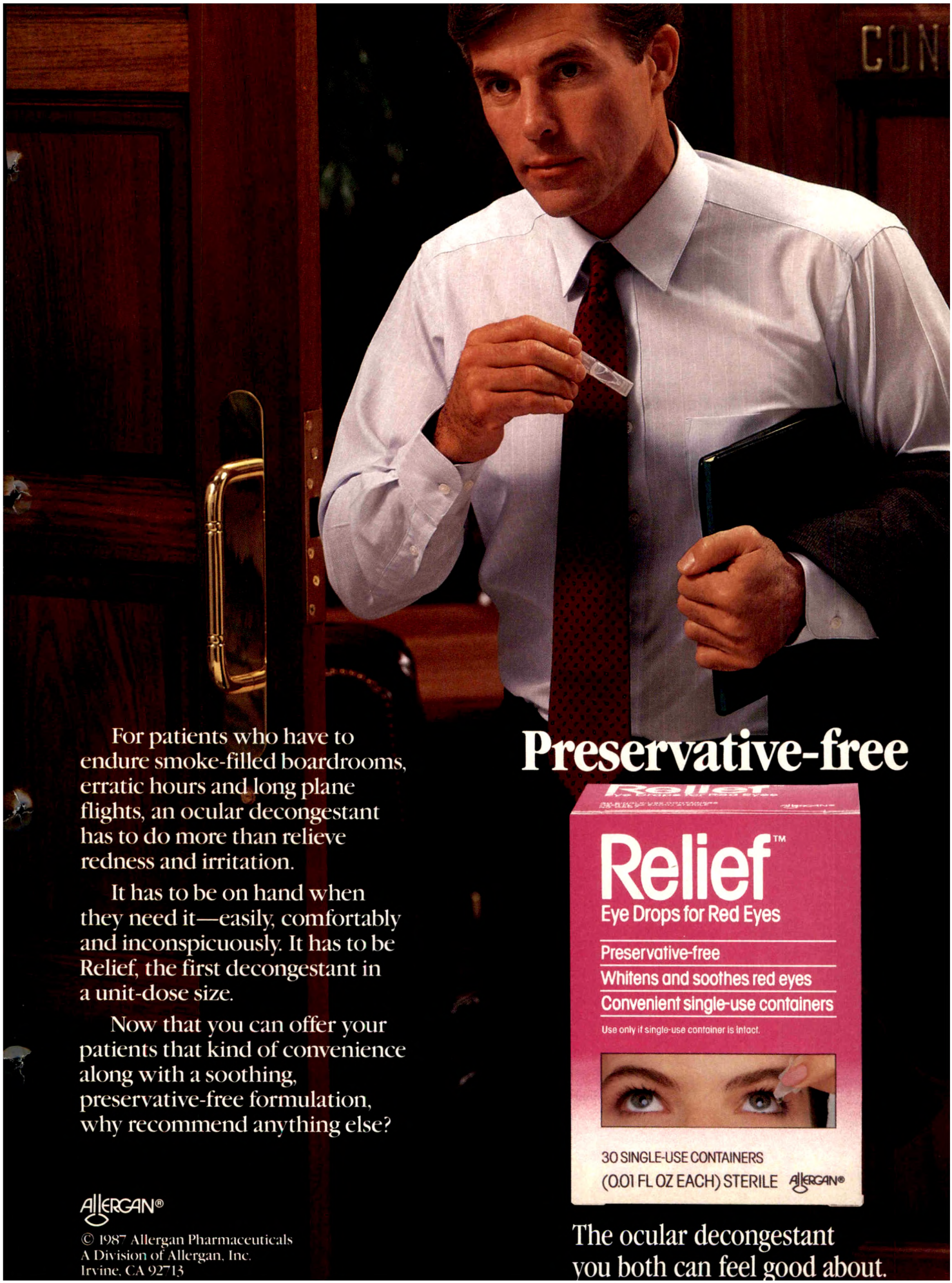
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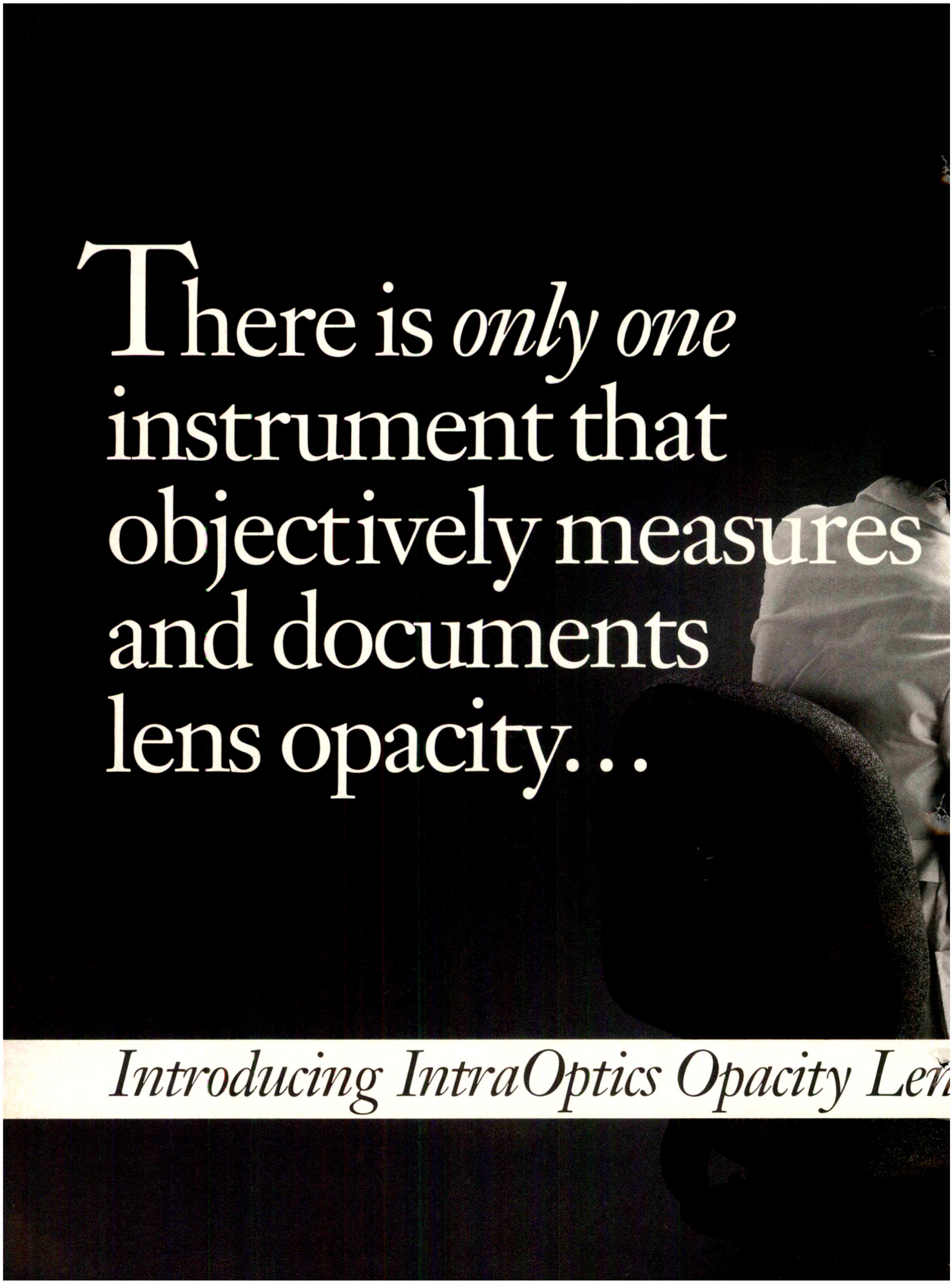
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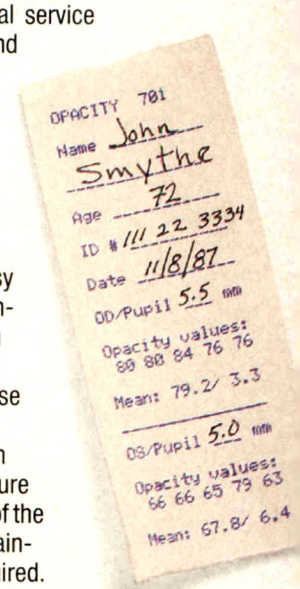
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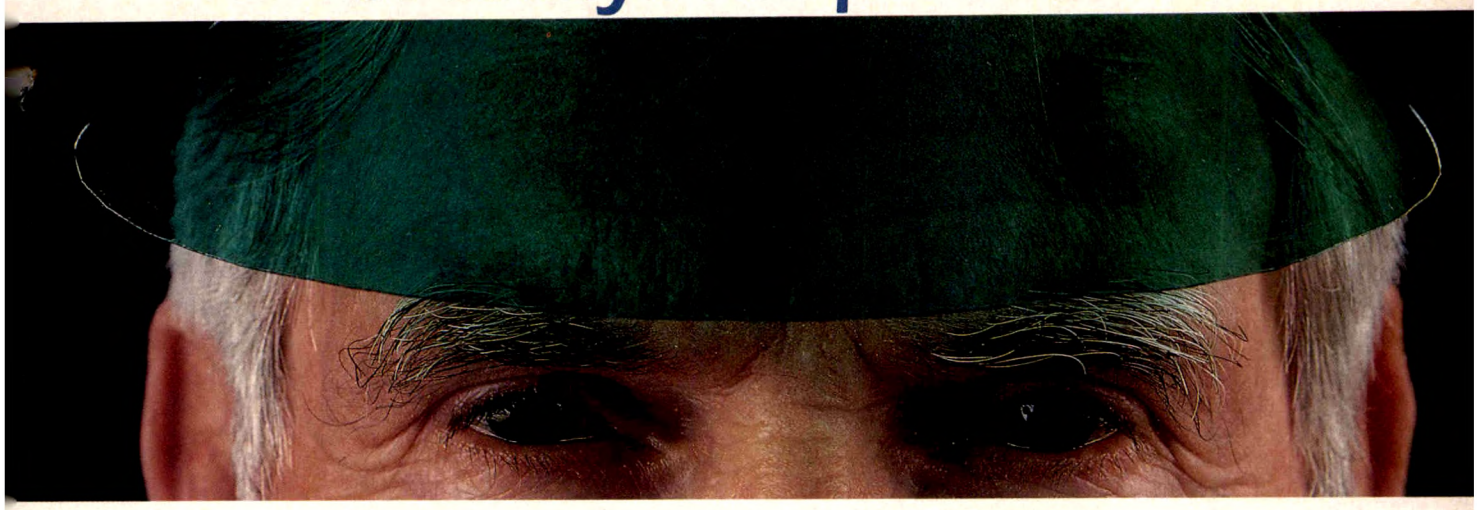
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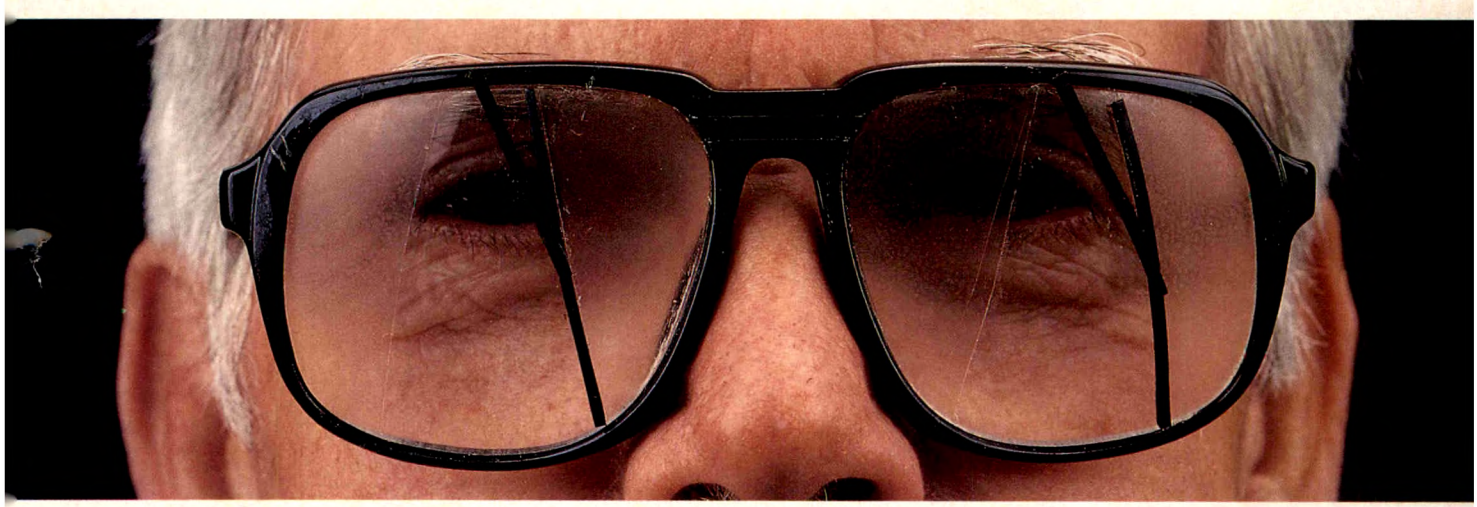
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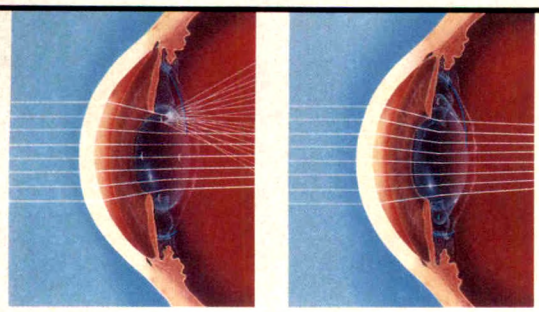


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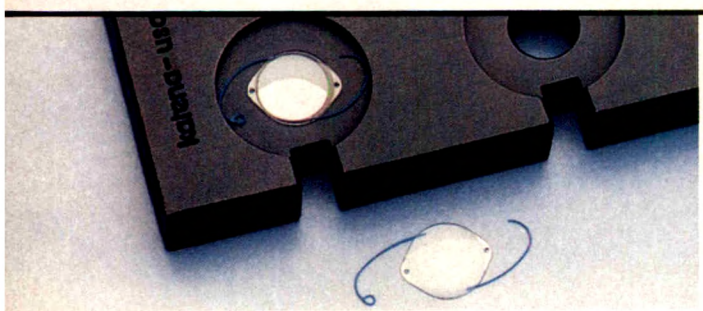
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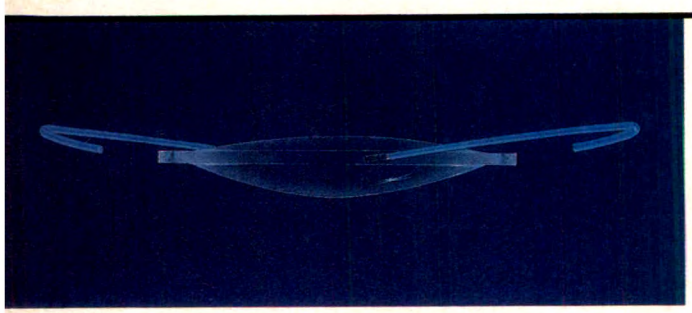
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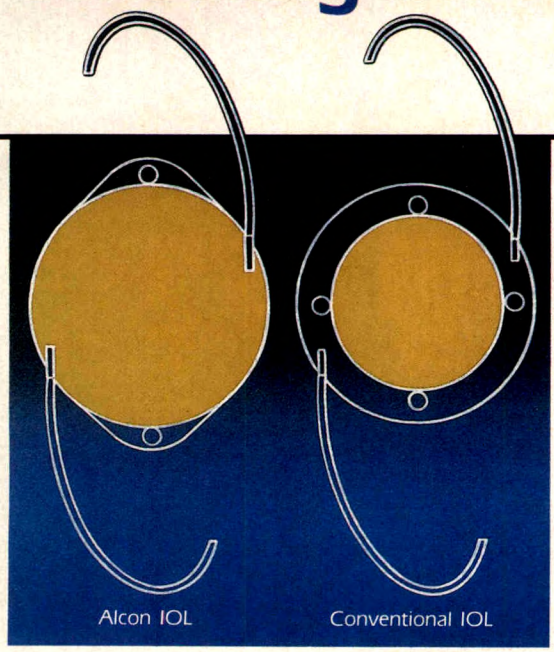
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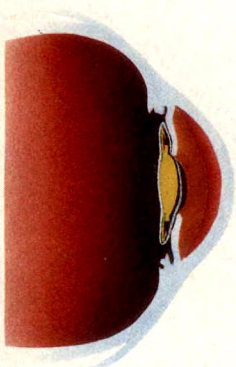


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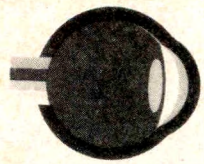
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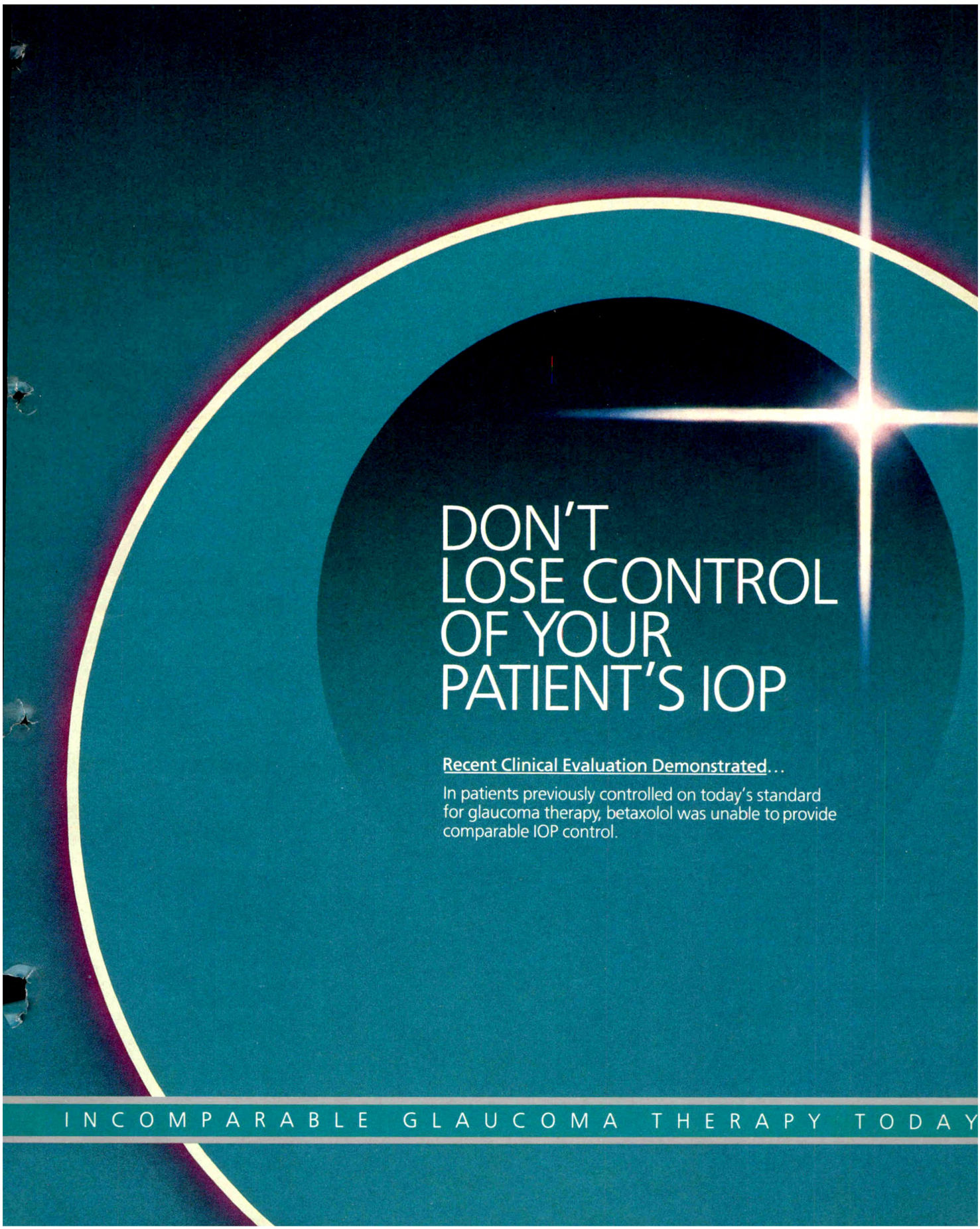
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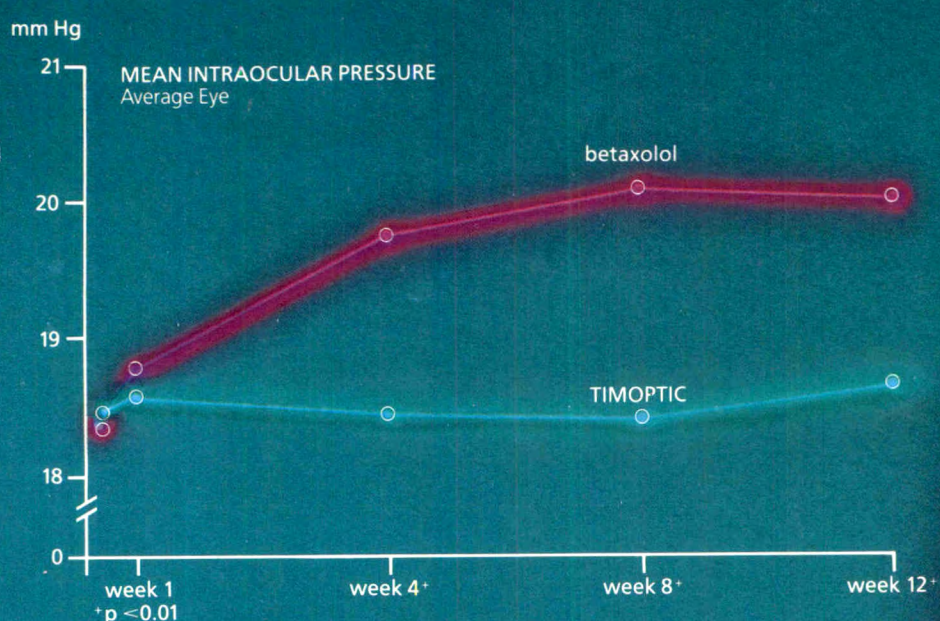

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As with the use of other antiglaucoma drugs, diminished responsiveness to TIMOPTIC after prolonged therapy has been reported in some patients. However, in one long-term study in which 96 patients have been followed for at least 3 years, no significant difference in mean IOP has been observed after initial stabilization.

TIMOPTIC is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; and hypersensitivity to any component of this product.

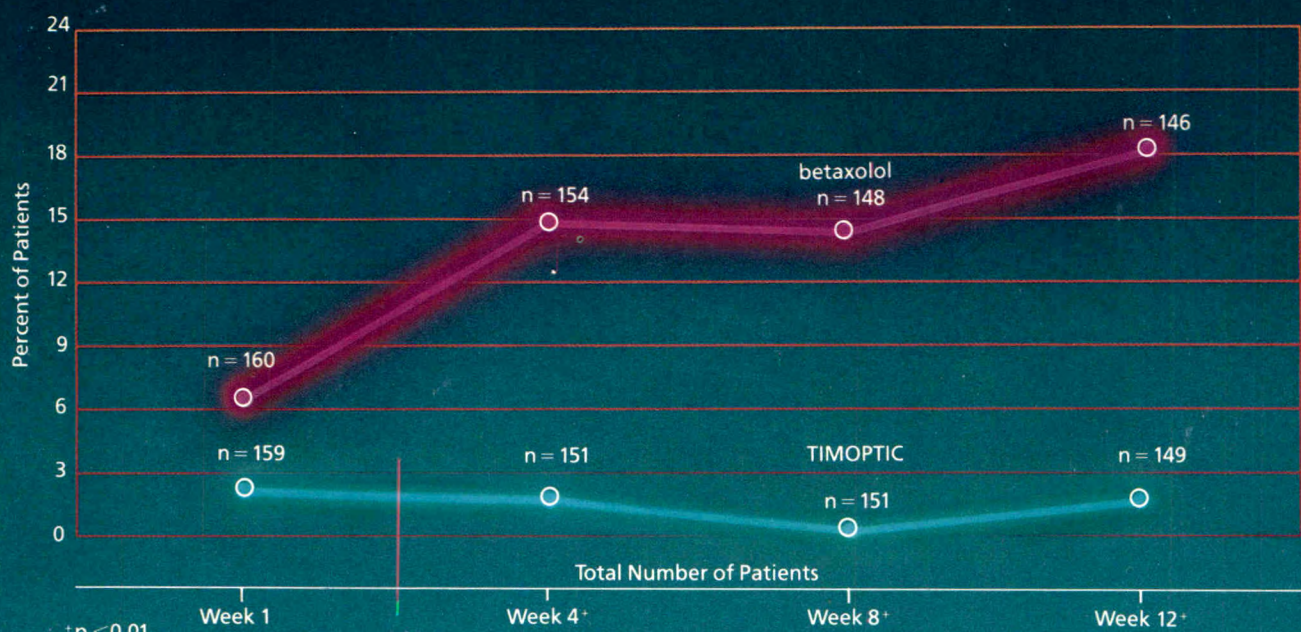
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How to start patients on TIMOPTIC:
Usual starting dosage: one drop 0.25% TIMOPTIC in the affected eye(s) twice a day.

How to transfer from another topical ophthalmic beta-adrenergic blocking agent to TIMOPTIC:

1. On the first day, after proper dosing, discontinue the topical agent being used.

2. On the second day, start treatment with one drop of 0.25% TIMOPTIC in the affected eye(s) b.i.d.

How to transfer from a single antiglaucoma agent (other than a topical ophthalmic beta-adrenergic blocking agent) to TIMOPTIC:

1. On the first day, continue with the agent already being used and add one drop 0.25% TIMOPTIC in the affected eye(s) b.i.d.

2. On the second day, discontinue the previously used agent and continue with TIMOPTIC in the affected eye(s) b.i.d.

How to transfer from several concomitantly administered antiglaucoma agents to TIMOPTIC:

1. If any agent is an ophthalmic beta-adrenergic blocker, discontinue before starting TIMOPTIC.

2. Continue the other agents being used, but add one drop of 0.25% TIMOPTIC to the affected eye(s) b.i.d.

3. On the following day, discontinue one of the other antiglaucoma agents.

4. The remaining antiglaucoma agents may be decreased or discontinued according to the patient's response to treatment.

If clinical response is not adequate:
Dosage may be increased (from the 0.25% solution) by changing to one drop 0.5% TIMOPTIC twice a day in the affected eye(s). Dosages above one drop of 0.5% TIMOPTIC twice a day generally have not been shown to produce further reduction of IOP. If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s).

In patients with a history of severe cardiac disease, signs of cardiac failure should be watched for and pulse rates should be checked.

CONTRAINDICATIONS: TIMOPTIC is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to any component of this product.

WARNINGS: As with other topically applied ophthalmic drugs, this drug may be absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death in association with cardiac failure, have been reported following administration of TIMOPTIC (see CONTRAINDICATIONS).

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, TIMOPTIC should be discontinued.

Obstructive Pulmonary Disease: PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (e.g., CHRONIC BRONCHITIS, EMPHYSEMA) OF MILD OR MODERATE SEVERITY, BRONCHOSPASTIC DISEASE OR HISTORY OF BRONCHOSPASTIC DISEASE (OTHER THAN BRONCHIAL ASTHMA OR HISTORY OF BRONCHIAL ASTHMA, IN WHICH 'TIMOPTIC' IS CONTRAINDICATED, see CONTRAINDICATIONS), SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS, INCLUDING 'TIMOPTIC'. However, if TIMOPTIC is necessary in such patients, then the drug should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution to patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

PRECAUTIONS: *General:* Patients who are receiving a beta-adrenergic blocking agent orally and TIMOPTIC should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Patients should not receive two topical ophthalmic beta-adrenergic blocking agents concurrently.

Because of potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with TIMOPTIC, alternative therapy should be considered.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. TIMOPTIC has little or no effect on the pupil. When TIMOPTIC is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone.

As with the use of other antiglaucoma drugs, diminished responsiveness to TIMOPTIC® (Timolol Maleate, MSD) after prolonged therapy has been reported in some patients. However, in one long-term study in which 96 patients have been followed for at least three years, no significant difference in mean intraocular pressure has been observed after initial stabilization.

Drug Interactions: Although TIMOPTIC used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with TIMOPTIC and epinephrine has been reported occasionally.

Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Caution should be used in the coadministration of beta-adrenergic blocking agents, such as TIMOPTIC, and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Animal Studies: No adverse ocular effects were observed in rabbits and dogs administered TIMOPTIC topically in studies lasting one and two years respectively.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year oral study of timolol maleate in rats, there was a statistically significant ($p < 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human oral dose* (1 mg/kg/day). Similar differences were not observed in rats administered oral doses equivalent to 25 or 100 times the maximum recommended human oral dose. In a lifetime oral study in mice, there were statistically significant ($p < 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages up to 60 mg timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p < 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/mL). In Ames tests, the highest concentrations of timolol employed, 5000 or 10,000 μg/plate, were associated with statistically significant elevations ($p < 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human oral dose.

Pregnancy: Pregnancy Category C: Teratogenicity studies with timolol in mice and rabbits at doses up to 50 mg/kg/day (50 times the maximum recommended human oral dose) showed no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (1,000 times the maximum recommended human oral dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 100 times the maximum recommended human oral dose, in this case without apparent maternotoxicity. There are no adequate and well-controlled studies in pregnant women. TIMOPTIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established by adequate and well-controlled studies.

ADVERSE REACTIONS: TIMOPTIC Ophthalmic Solution is usually well tolerated. The following adverse reactions have been reported either in clinical trials of up to three years' duration prior to release in 1978 or since the drug has been marketed.

BODY AS A WHOLE: Headache, asthenia, chest pain. CARDIOVASCULAR: Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cardiac failure, palpitation, cardiac arrest. DIGESTIVE: Nausea, diarrhea. NERVOUS SYSTEM/PSYCHIATRIC: Dizziness, depression, increase in signs and symptoms of myasthenia gravis, paresthesia. SKIN: Hypersensitivity, including localized and generalized rash, urticaria. RESPIRATORY: Bronchospasm (predominantly in patients with preexisting bronchospastic disease), respiratory failure, dyspnea, nasal congestion. ENDOCRINE: Masked symptoms of hypoglycemia in insulin-dependent diabetics (see WARNINGS). SPECIAL SENSES: Signs and symptoms of ocular irritation, including conjunctivitis; blepharitis; keratitis; blepharoptosis; decreased corneal sensitivity; visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases); diplopia; ptosis.

Causal Relationship Unknown: The following adverse effects have been reported, and a causal relationship to therapy with TIMOPTIC has not been established: *Body as a Whole:* Fatigue; *Cardiovascular:* Hypertension, pulmonary edema, worsening of angina pectoris; *Digestive:* Dyspepsia, anorexia, dry mouth; *Nervous System/Psychiatric:* Behavioral changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence, and other psychic disturbances; *Skin:* Alopecia; *Special Senses:* Aphakic cystoid macular edema; *Urogenital:* Retroperitoneal fibrosis, impotence.

The following additional adverse effects have been reported in clinical experience with oral timolol maleate and may be considered potential effects of ophthalmic timolol maleate: *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Edema, worsening of arterial insufficiency, Raynaud's phenomenon, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting; *Hematologic:* Nonthrombocytopenic purpura; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating, cold hands and feet; *Musculoskeletal:* Arthralgia, claudication; *Nervous System/Psychiatric:* Vertigo, local weakness, decreased libido, nightmares, insomnia, diminished concentration; *Respiratory:* Rales, cough, bronchial obstruction; *Special Senses:* Tinnitus, dry eyes; *Urogenital:* Urination difficulties.

Potential Adverse Effects: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents and may be considered potential effects of ophthalmic timolol maleate: *Digestive:* Mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Agranulocytosis, thrombocytopenic purpura; *Nervous System:* Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Urogenital:* Peyronie's disease.

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis sicca, otitis, and sclerosing serositis attributed to the beta-adrenergic receptor blocking agent practolol. This syndrome has not been reported with timolol maleate.

HOW SUPPLIED: TIMOPTIC Ophthalmic Solution, 0.25% and TIMOPTIC Ophthalmic Solution, 0.5%. Both are available in 2.5-mL, 5-mL, 10-mL, and 15-mL plastic OCUMETER* ophthalmic dispensers with a controlled drop tip. **Also Available:** Preservative-free TIMOPTIC in OCUDOSE* (Dispenser) Sterile Ophthalmic Unit-Dose Dispenser (see separate Prescribing Information).

Storage: Protect from light. Store at room temperature.

*The maximum recommended single oral dose is 30 mg of timolol. One drop of TIMOPTIC 0.5% contains about 1/150 of this dose, which is about 0.2 mg.

MSD
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For more detailed information, consult your MSD Representative and the Prescribing Information.
Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

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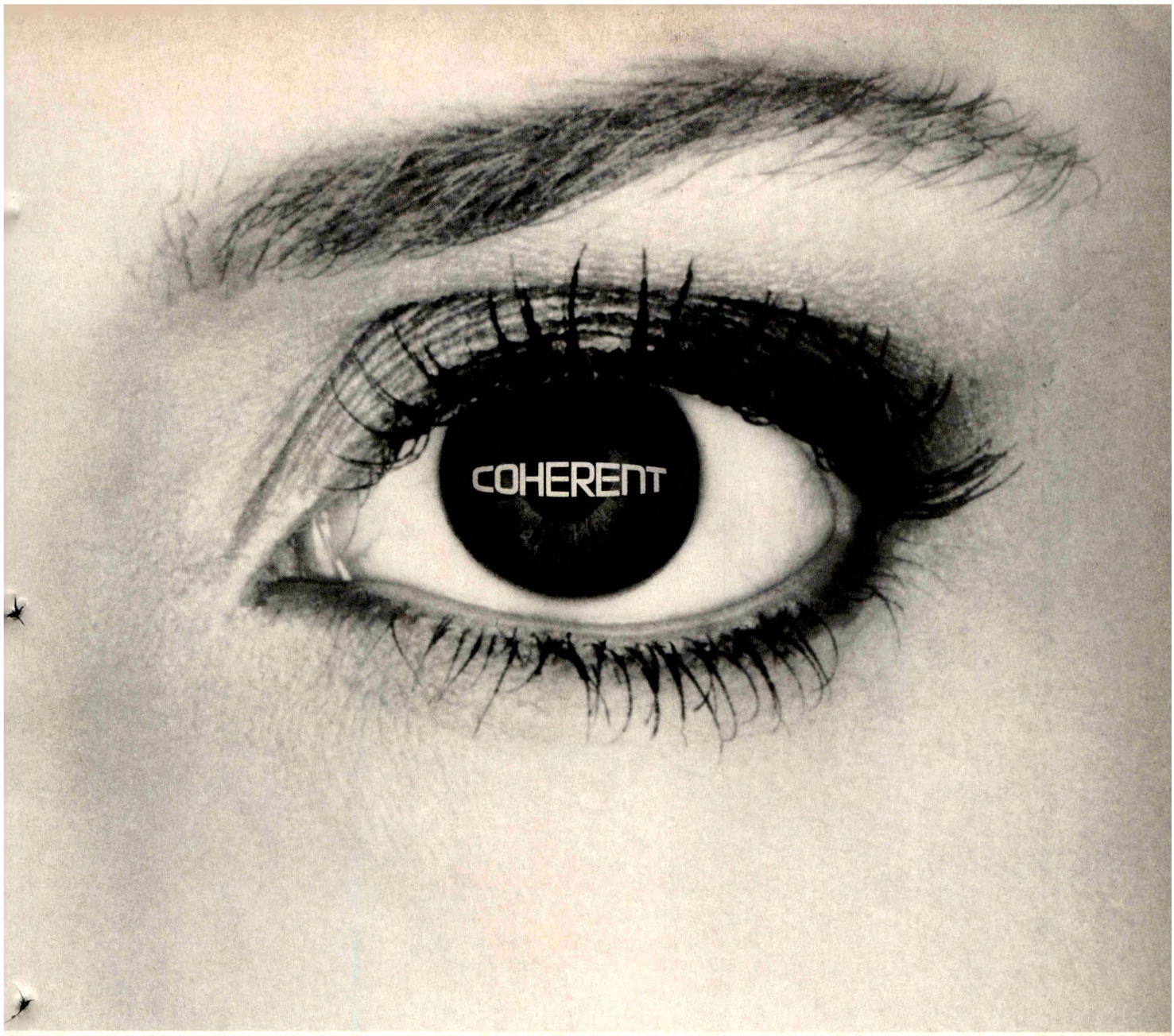
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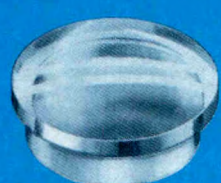




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Theo Seiler, M.D., T. Bende, Ph.D., J. Wollensak, M.D., and Stephen Trokel, M.D.

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© American Journal of Ophthalmology 105:117–124, February, 1988

Sensorineural Hearing Loss in Patients With Typical Retinitis Pigmentosa

James M. McDonald, Sc.D., David A. Newsome, M.D., and William F. Rintelmann, Ph.D.

We performed detailed audiologic testing in 45 patients with retinitis pigmentosa and 45 age- and sex-matched controls. Ten (22%) of the retinitis pigmentosa patients had a sensorineural hearing loss that varied from mild to severe. None of the control subjects had a hearing loss. Audiograms measured over a ten- to 30-year period were available for four patients with retinitis pigmentosa and each showed progressive hearing loss. The results indicate the important role of audiologic evaluation in treating patients with retinitis pigmentosa.

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The Relation of Rhodopsin and Scotopic Retinal Sensitivity in Sector Retinitis Pigmentosa

Anne B. Fulton, M.D., and Ronald M. Hansen, Ph.D.

We used reflection retinal densitometric, psychophysical, and electroretinographic techniques to study the scotopic retinal function of a mother and her three daughters who had clinical evidence of a sectoral type of retinitis pigmentosa. Retinal regions with, and those without, ophthalmoscopic signs of degeneration were investigated. During dark adaptation, the time courses of rhodopsin regeneration and recovery of scotopic sensitivity were similar to normal as was the relation of rhodopsin to scotopic threshold. In dark-adapted eyes, threshold increases were not proportional to rhodopsin loss. The results of psychophysical tests of background adaptation and temporal summation, and analysis of the relation of electroretinographic a- to b-wave amplitudes, led to the conclusion that abnormalities of photoreceptor cell function central to the rhodopsin-bearing outer segments accounted for the increased thresholds.

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Low-Contrast Letter Charts to Detect Subtle Neuropathies

Mitchell D. Drucker, M.D., Peter J. Savino, M.D., Robert C. Sergott, M.D., Thomas M. Bosley, M.D., Norman J. Schatz, M.D., and Paul S. Kubilis, M.S.

We performed visual contrast sensitivity testing with Regan's low-contrast letter charts on 30 patients with optic neuropathies and good Snellen visual acuity. Results of this testing were compared with color vision and the presence of an afferent pupillary defect. Regan's low-contrast letter charts were found to be 93% sensitive for detecting subtle optic neuropathies, with the apparent false-negative findings being readily explainable. Color vision testing was abnormal in only 49% of eyes with known optic neuropathies.

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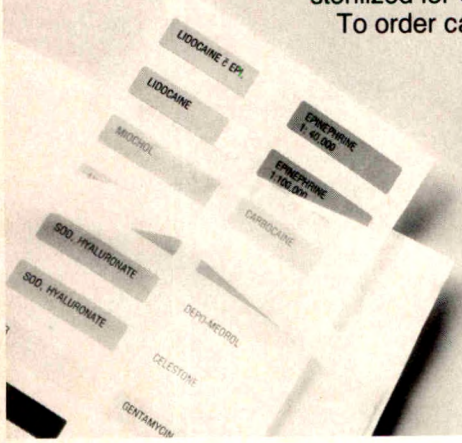
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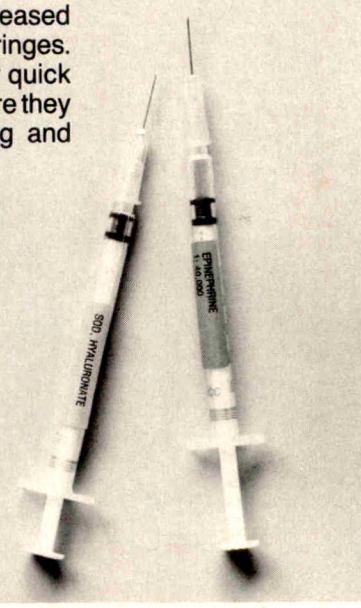
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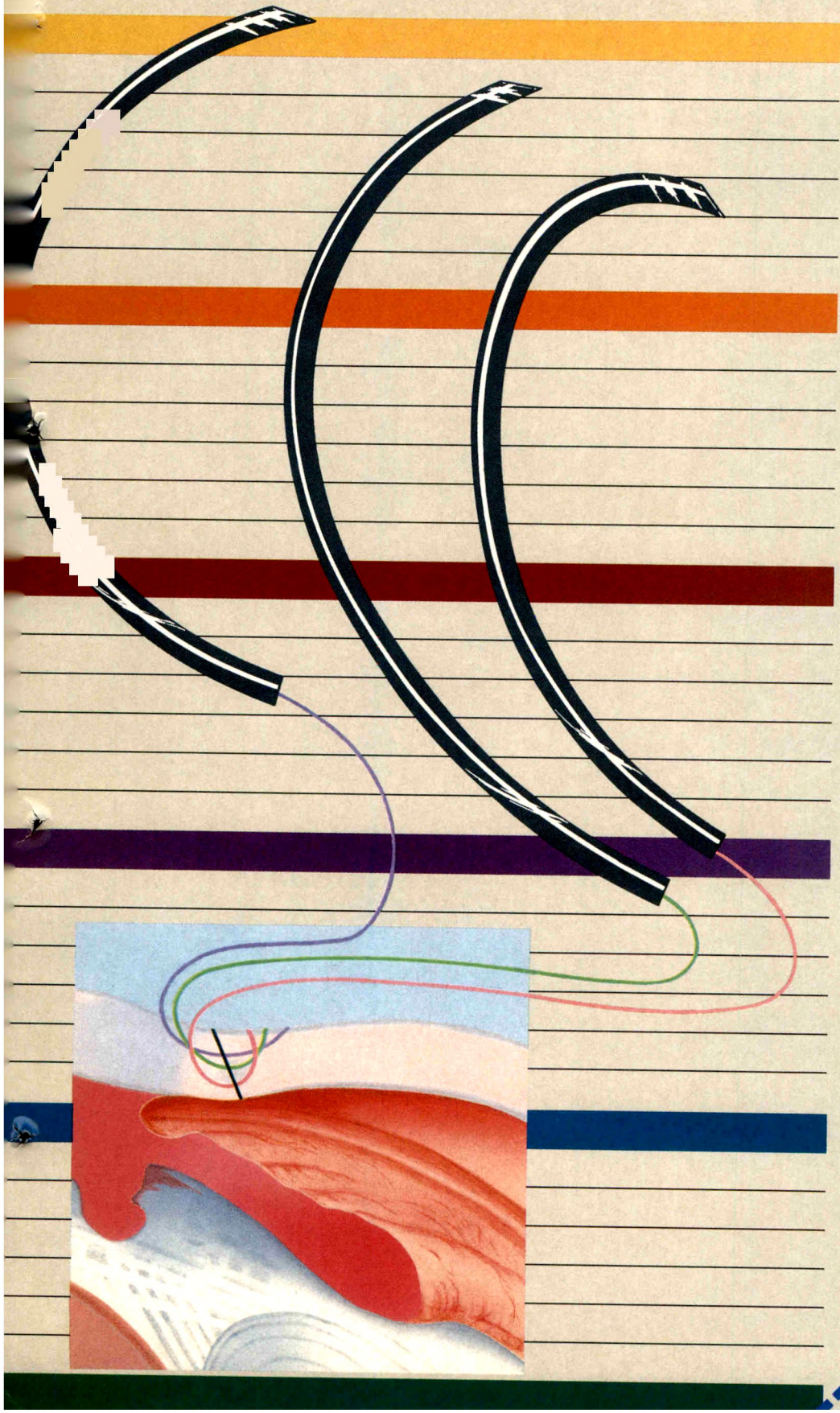
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Ganglioglioma of the Optic Nerve

Donald J. Bergin, M.D., Thomas E. Johnson, M.D., William H. Spencer, M.D., and Clinton D. McCord, M.D.

We examined a 15-year-old boy who had a ganglioglioma involving the left optic nerve, which caused proptosis, decreased vision, and optic atrophy. Computed tomography demonstrated an intraconal mass along the course of the orbital portion of the optic nerve. The only evidence of systemic neurofibromatosis was axillary freckling. The patient underwent a combined medial and lateral orbitotomy and excision of the tumor. Histologic examination demonstrated a mass composed of neurons and glial cells characteristic of ganglioglioma. After a one-year follow-up period, we have found no evidence of recurrence.

© American Journal of Ophthalmology 105:146–149, February, 1988

A Double-Masked Comparison of Carteolol and Timolol in Ocular Hypertension

Barrett Scoville, M.D., Brigitte Mueller, B. G. White, Ph.D., and Gunter K. Krieglstein, M.D.

We performed a double-masked study in which 98 patients with ocular hypertension who had been previously treated with timolol received either timolol 0.25% or carteolol 1%, a beta-blocker with intrinsic sympathomimetic activity. The drugs were administered topically twice daily for one month after a one-week washout period. Intraocular pressure was measured at baseline and after one and four weeks of treatment. The appearance of the fundus, external eye, visual fields, tear secretion, blood pressure, and pulse were recorded. Adverse symptoms were elicited using a menu-type questionnaire and an overall judgment of therapy was recorded. Carteolol was as effective as timolol in reducing intraocular pressure. There were significantly fewer patients reporting adverse events overall ($P = .019$), and eye irritation specifically ($P = .02$), in the group treated with carteolol.

© American Journal of Ophthalmology 105:150–154, February, 1988

Sustained Reduction of Intraocular Pressure in Humans With the Calcium Channel Blocker Verapamil

Mark B. Abelson, M.D., C. Mitchell Gilbert, M.D., and Lisa M. Smith, B.S.

We investigated the effect of the calcium channel blocker verapamil on intraocular pressure in human volunteers. In the initial trial, 15 subjects with untreated ocular hypertension were tested. After a baseline measurement was obtained with applanation tonometry, a 40-μl drop of verapamil, 1.25 mg/ml, was instilled in one eye. After 30 minutes, a second reading was taken. In a subsequent trial of 12 untreated ocular hypertensive subjects, the duration of action was determined using the same dose and method of delivery. Results showed that verapamil elicited a mean ± S.E.M. change in intraocular pressure of -3.8 ± 0.900 mm Hg in the treated eye, and -1.6 ± 0.400 mm Hg in the untreated eye. This reduction was statistically different in both eyes (treated eye, $P = .0007$; untreated eye, $P = .005$). This decrease in intraocular pressure remained statistically significant when compared to predrug baseline values for up to ten hours.

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Nuclear Sclerosis After Vitrectomy for Idiopathic Epiretinal Membranes

Serge de Bustros, M.D., John T. Thompson, M.D., Ronald G. Michels, M.D., Cheryl Enger, M.S., Thomas A. Rice, M.D., and Bert M. Glaser, M.D.

We performed a retrospective analysis of lens changes occurring after vitrectomy for idiopathic epiretinal membranes causing macular pucker on 75 consecutive phakic eyes. Thirty-five eyes (47%) had appearance or progression of nuclear sclerosis. There were no changes in anterior subcapsular cataracts and three eyes (4%) had minimal changes in posterior subcapsular cataracts.

Based on univariate analysis, presence of preoperative nuclear sclerosis, length of follow-up period, and surgeon were found to be associated with the occurrence or progression of nuclear sclerosis. Differences between surgeons were largely accounted for by the difference in proportions with preoperative nuclear sclerosis, and differing lengths of follow-up. Kaplan-Meier life table analysis performed on 53 eyes with examination of fellow eyes and longer follow-up showed significantly more nuclear sclerosis in the operated on eye when compared to the fellow eye (log-rank test, $P < .0001$).

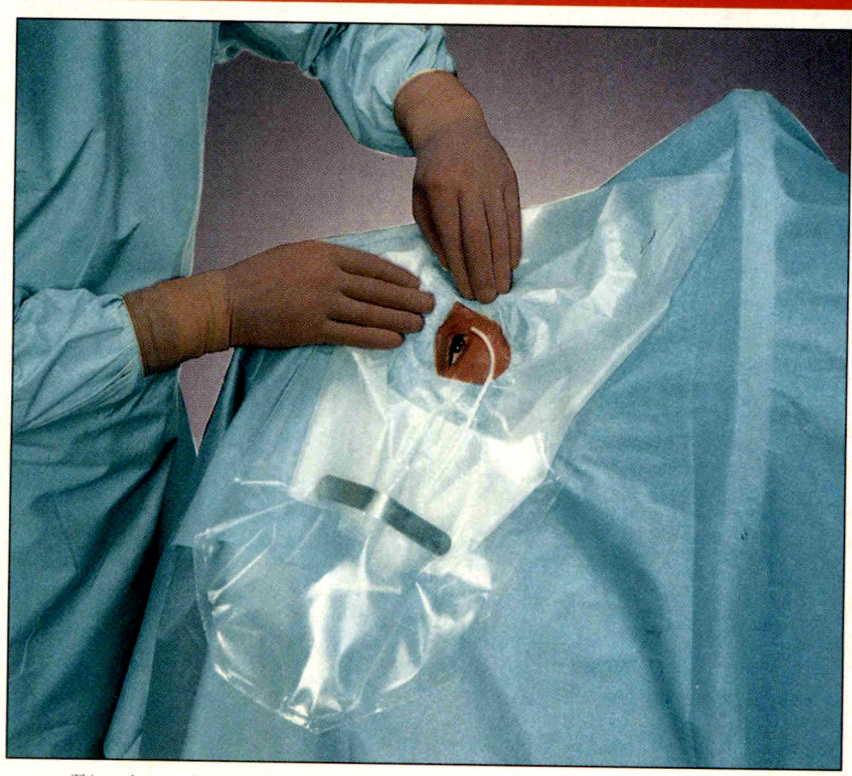
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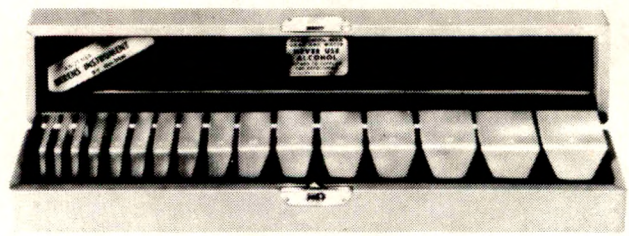
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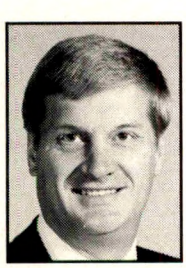
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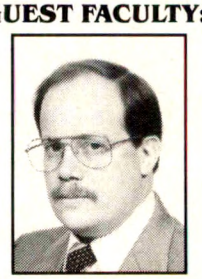
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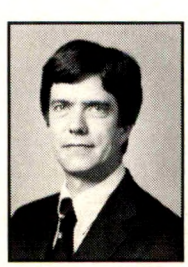
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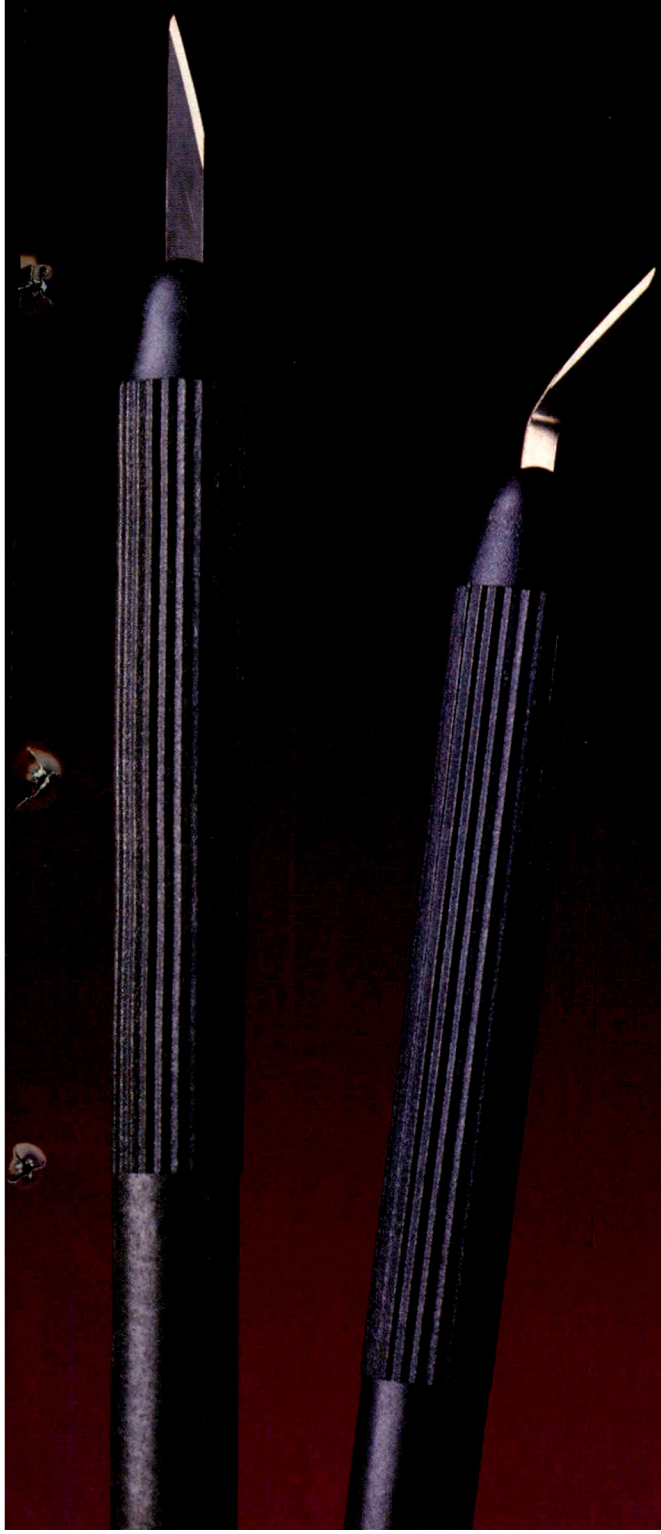
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AMERICAN JOURNAL OF OPHTHALMOLOGY®

VOLUME 105 NUMBER 2 FEBRUARY, 1988

Excimer Laser Keratectomy for Correction of Astigmatism

Theo Seiler, M.D., T. Bende, Ph.D., J. Wollensak, M.D., and Stephen Trokel, M.D.

We treated 13 eyes (12 patients) with excimer laser surgery for correction of astigmatism using linear corneal T-excisions. All eyes were followed up for a minimum of three months. We used a newly developed delivery system and special contact masks to deliver the 193-nm excimer light. Astigmatic corrections of up to 4.16 diopters were obtained. The actual corrections corresponded well with the intended values as predicted by a biomechanical theory. The refractive change over time was different than that observed after knife incisions, suggesting different repair mechanisms. An epithelial plug filling the whole T-excision persisted for over one year in all eyes.

THE CONCEPT OF surgical control of corneal astigmatism can be traced to Schiøtz in 1885.[1] For the past several years refractive surgery has been promoted in the United States and Russia, but its acceptance has been limited because of the poor predictability of the final optical results as well as resulting glare from incisions that encroach on the optical zone. When treating myopia, adequate results are obtained only in eyes with minimal refractive error. In myopia greater than 5 diopters, 6% of the patients become more than 1 diopter hyperopic and 30% are more than 2 diopters undercorrected.[2]

In theory, the incision depth is the most critical factor in determining the refractive outcome.[3] For this reason, it is not surprising that techniques that rely on corneal incisions created by steel or diamond knives yield inconsistent results. This inconsistency occurs because these corneal incisions have been found to vary considerably from the expected depth, with ranges from 66% to 96% for steel and 61% to 98% for diamond knife incisions.[4] With laser keratectomy, however, the depth of corneal excisions can be more accurately controlled. Each individual laser pulse excises a specific amount (0.2 to 1.0 μm) of corneal tissue,[5] which determines the depth of the keratectomy. Thus, in theory, the depth of excised tissue is uniform and predictable to an accuracy of less than 1 μm throughout its length, provided that the energy distribution is homogenous across the laser beam. The primary corneal locus of astigmatism suggests that surgical intervention for astigmatism has a more pressing indication than other refractive errors, especially given the limited ability of spectacle or contact lens technology to compensate for large astigmatic errors.

Herein we present the clinical results of astigmatism correction surgery with the excimer laser and compare them with a biomechanical model we developed. The surgical procedure used emulates the T-incision. However, we prefer the term "T-excision" because excimer laser photoablation cleanly removes a narrow strip of tissue, which is more accurately described as an excision or keratectomy.

Beginning in July 1985, before initiation of the study, we performed a variety of corneal laser excisions in 20 patients with blind eyes. The results of this pilot study indicated that rapid epithelial healing with stabilization of corneal topography occurred within six weeks of the laser surgery and remained stable for more than one year. Because of these favorable observations, we believed that the application

Accepted for publication Nov. 11, 1987.

From the Universitätsaugenklinik im Klinikum Charlottenburg, Berlin, West Germany (Drs. Seiler, Bende, and Wollensak), and the Edward S. Harkness Eye Institute, Columbia-Presbyterian Medical Center, New York (Dr. Trokel).

Reprint requests to Theo Seiler, M.D., Universitätsaugenklinik im Klinikum Charlottenburg, Spandauer Damm 130, 1000 Berlin 19, West Germany.

of linear laser excisions for the correction of refractive errors was justified and a study of T-excisions should be undertaken, initially in blind eyes and then in a clinical study of laser keratectomy in sighted astigmatic eyes. As most of the blind eyes did not show astigmatism originally, astigmatism was induced in some eyes by a T-excision procedure.

Patients and Methods

Beginning Oct. 1, 1986, we treated eight blind eyes with excimer laser T-excision keratectomies (Patients 1 through 8). The mean age of these patients was 66 years (range, 41 to 86 years). Three eyes had choroidal melanoma, two of which have now been enucleated, one eye had been blinded by a central retinal arterial occlusion, and four eyes had absolute glaucoma. The favorable results we obtained in this group of patients led us, on Jan. 15, 1987, to begin a clinical investigation of laser T-excisions on five severely astigmatic sighted eyes (Patients 9 through 12), in whom contact lenses had failed. The first patient (Patient 9, left eye) had 4 diopters of astigmatism. After three months, three additional patients were treated, all with a greater degree of astigmatism. Patient 11 had an astigmatism of 6.5 diopters after cataract extraction. Informed consent was obtained from all patients in this study.

Biomicroscopy and applanation tonometry were performed on each patient. However, keratometry was the most important measurement obtained in evaluating the surgical results. A keratometer was used to measure the preoperative and postoperative corneal curvatures. The sighted eye of the blind patients was used with an alternative fixation target. The position of this fixation target remained constant. Clinical data were obtained preoperatively, and on postoperative days 1, 3, and 7 (early postoperative period). Late postoperative examinations were performed at one, three, and six months.

Laser keratectomy was performed using a prototype laser system (Fig. 1) developed in cooperation with Lambda Physik and Carl Zeiss. The system consists of a surgical microscope physically and optically coupled to the excimer laser to provide coaxial laser delivery within the operative field. The laser was configured as an unstable resonator and run exclusively with argon and fluorine gas fills to produce 193-nm light. The laser pulse width is 15 nsec and the laser firing rate is adjustable to 100 Hz. The laser output is adjusted by regulating the initiating breakthrough voltage of the laser so that the fluence measures 165 mJ/cm^2 at the corneal surface. The repetition rate used was 30 Hz and the number of laser pulses was controlled by a microprocessor. Treatment was initiated by a footswitch to the preset variables.

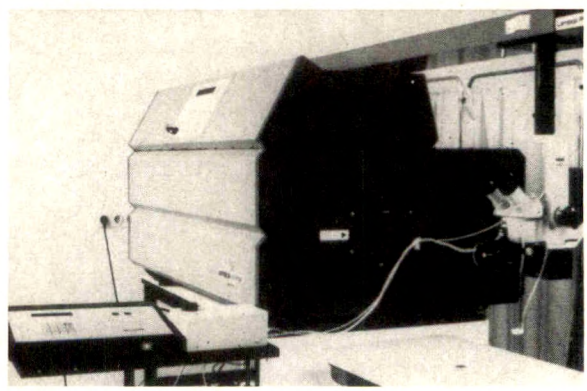


Fig. 1 (Seiler and associates). Excimer laser and delivery system. The terminal that controls laser repetition rate and the total number of pulses is adjacent to the laser.

The depth of the excision can be calculated from the known ablation rate of the 193-nm laser at the measured fluence. However, the ablation of a rabbit cornea was used as a daily biologic check.

To compensate for small eye movements, we developed a perforated and precut hard contact lens that functions as a mask to shape the laser light that reaches the cornea. These contact lenses were constructed of polymethylmethacrylate coated with a metal foil chosen to reflect ultraviolet radiation. The two precut tangential slits were placed 3 mm to either side of the lens center, leading to a 6-mm central optical zone. Each slit measured 4.5 mm long by 150 μm wide. The polymethylmethacrylate lens slits were made by the focused output of the excimer laser followed by the microscopic manual removal of the overlying foil.

A topical anesthetic was instilled. The central thickness of the cornea was measured by ultrasonic pachymetry. Because corneal thickness increases peripherally and the laser beam is not perpendicular to the surface at the point of irradiance, the value of central corneal thickness was increased by a factor of 1.18.[6] With this corrected corneal thickness and the estab-

lished ablation depth per pulse (for example, 0.32 μm), we calculated the total number of pulses necessary to obtain the planned percentage corneal thickness excision. This number was then entered into the laser control terminal.

After marking the central cornea at the slit lamp with an indentation ring, the patient was placed in a supine position on a gurney so the patient's eye was centered under the microscope and the excimer laser delivery system. An eyelid speculum was inserted and the contact lens was centered visually on the cornea, with the large diameter of the contact lens centered on the marks produced by the indentation ring. The cornea was not irrigated. This dehydration of the corneal surface helps maintain position of the contact lens mask and prevents fluid from filling the excision sites or the mask slits, which would block the laser beam. The eye was then stabilized by a Thornton ring and adjusted so that one slit of the mask lay within the field of irradiation (1 × 6 mm). This guarantees the independence of excision depth on small eye movements. After laser light exposure (typically 50 seconds), the same procedure was used for the other slit. Both T-excision sites were irrigated with balanced salt solution immediately upon removal of the mask. After instillation of dexamethasone 0.1% and gentamicin 0.3% eyedrops, the eye was patched for one day.

The complete procedure took about 15 minutes, although the excimer exposure time was less than 1 minute for each excision. After removal of the patch, topical dexamethasone and gentamicin were used three times daily for one week. The excision depths were estimated by evaluating slit-lamp photographs (Fig. 2), with a measurement error of ±8%, and determined histologically in those eyes that were enucleated.

To evaluate the change in astigmatism induced by the T-excisions, the alterations in corneal curvature were calculated by using the axiom of Euler.[7] The total amount of astigmatic change (D_{tot}) was determined by calculating the net power changes in the orthogonal corneal axes parallel and perpendicular to the treatment meridian:

$$D_{tot} = D_{perp} - D_{para},$$

where D_{perp} is the change in diopters in meridian perpendicular to the excisions and D_{para} is the change in diopters in the meridian parallel to the excisions.

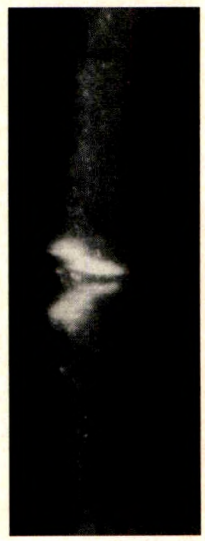


Fig. 2 (Seiler and associates). Patient 9, left eye. Slit-lamp photograph of an excimer excision five weeks after surgery. The excision depth was estimated to be 90 ± 8% of corneal thickness.

The theory predicts flattening of the cornea in the perpendicular axis and steepening in the parallel axis. The meridian perpendicular to the excisions is called the excision axis (Table).

Results

In all cases the expected flattening in the perpendicular axis and steepening in the parallel axis was documented (Table). In the first postoperative week, corneal astigmatism values fluctuated, but they tended to stabilize after two weeks (Fig. 3).

Biomicroscopy on the first postoperative day showed stromal edema surrounding the excision sites. The local edema resolved over two to four days, as the excision sites reepithelialized. By the third postoperative day, epithelium had grown into the excision sites, thus producing irregular margins (Figs. 4 and 5). In some cases the entire keratectomy was filled by an epithelial plug. In other eyes, even after one month, small slits remained patent between the epithelialized margins of the excised stroma.

Patients reported foreign body sensations and photophobia several days after the surgery. These subjective symptoms resolved over the first postoperative week in all but two patients in whom mild epiphora persisted for a second week. Glare persisted in three eyes for eight weeks. Fluctuations in visual acuity were not detected after one week. Visual acuity under glare conditions was not tested. Central corneal sensitivity was symmetric and normal in all eyes.

TABLE
CLINICAL DATA

PATIENT NO.*	OCULAR ABNORMALITY	PREOPERATIVE KERATOMETRY READING	EXCISION AXIS (DEG)	EXCISION DEPTH (%)	EARLY POSTOPERATIVE KERATOMETRY READING	LATE POSTOPERATIVE KERATOMETRY READING	FLATTENING (D_{PERP})	STEEPENING (D_{PARA})	TOTAL CHANGE (D_{TOT})
1	Melanoma†	42.1 +1.5 × 4	90	76	42.4 +1.7 × 55	Enucleated	−0.63	+1.43	−2.06
2	Melanoma‡	42.8 +1.2 × 3	90	57	43.4 +0.1 × 180	43.4 +0.3 × 80	−0.59	+0.89	−1.48
3	Absolute glaucoma	39.75 +5.5 × 108	0	92	40.5 +4.6 × 128	40.7 +4.0 × 130	−1.67	+2.07	−3.74
4	Absolute glaucoma	42.75 +0.75 × 99	90	87	42.1 +3.6 × 90	42.5 +3.9 × 93	−0.26	+2.91	−3.17
5	Absolute glaucoma	43.08 +1.3 × 85	90	93	41.75 +4.1 × 97	40.4 +5.6 × 97	−2.61	+1.55	−4.16
6	Central artery occlusion	43.5 +3.7 × 169	90	81	44.25 +1.9 × 170	44.75 +1.4 × 168	−0.98	+1.18	−2.16
7	Absolute glaucoma	40.17 +1.17 × 102	0	74	41.0 +0.75 × 5	—§	−0.29	+1.53	−1.82
8	Melanoma	42.08 +1.08 × 20	90	51	42.6 +0.2 × 75	42.8 +0.5 × 90	−0.21	+1.11	−1.32
9	Left eye, hyperopic astigmatism	39.5 +4.0 × 11	100	90	40.5 +2.3 × 15	40.7 +2.0 × 27	−0.97	+1.37	−2.34
	Right eye, hyperopic astigmatism	39.75 +3.5 × 1	90	80	40.75 +2.1 × 10	40.95 +1.9 × 15	−0.53	+1.33	−1.86
10	Astigmatism	42.5 +4.5 × 5	95	95	43.25 +0.5 × 115	43.75 +0.5 × 20	−2.78	+1.28	−4.06
11	Hyperopic astigmatism	39.5 +6.5 × 80	170	92	41.0 +3.75 × 75	41.25 +2.5 × 78	−2.25	+1.75	−4.0
12	Astigmatism	41.4 +4.17 × 10	100	91	42.9 +2.2 × 5	43.6 +0.7 × 8	−1.3	+2.18	−3.48

*Patients 1 through 8, blind eyes or enucleation intended; Patients 9 through 12, sighted eyes.
†Enucleated one week after excimer surgery.
‡Enucleated three months after excimer surgery.
§Patient lost to follow-up.

The histologic examination of excision depth in the two enucleated eyes showed agreement with the intended depth within ±5%, while the intended depth and the depth verified by slit-lamp micrographs showed coincidence within the measurement error of ±8%.

In three eyes with absolute glaucoma and high intraocular pressure after excimer surgery, the pressure dropped by 10 to 15 mm Hg before returning to the preoperative levels within three to four days. We could not detect any signs of a microperforation.

Discussion

Two experimental approaches have evolved for the clinical use of excimer laser technology for refractive surgery of the cornea. One approach uses the laser to create linear or circular excisions of corneal tissue, similar to conventional incision techniques. These incisions are planned to alter the mechanical stress pattern of the incised corneal stroma. In the untouched central cornea a new stress equilibrium is estab-

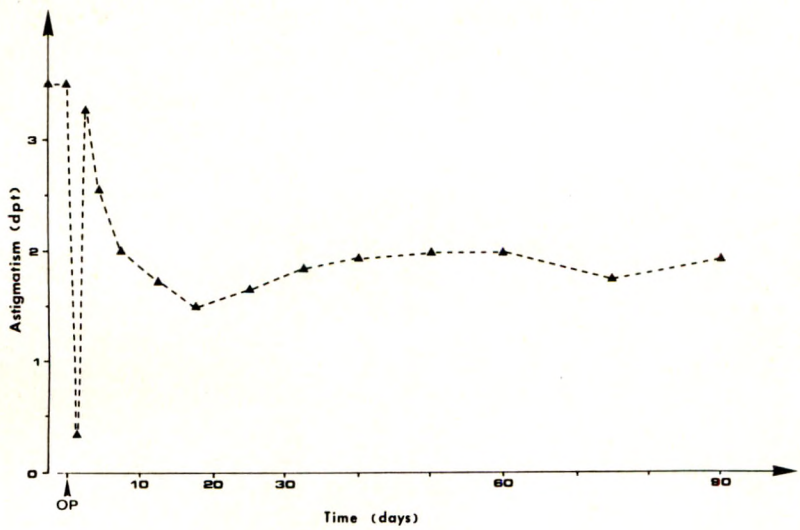


Fig. 3 (Seiler and associates). Patient 9, right eye. Change in astigmatism over time after excimer T-excision keratectomy. Refractive equilibrium was attained after one month. The rapid changes within the first postoperative days are believed to be the result of stromal edema.

lished, which produces a new optical curvature.

The other approach directly affects the optical center of the cornea. With this method, reported by Marshall and associates,[8] ablation of tissue from the central surface of the cornea defines a new refractive surface. However, surgery of the central corneal zone risks degradation of the corneal optics during the ablation or healing of the collagen lamellae. This technique has the advantages of being relatively insensitive to intraoperative motion artifacts and of

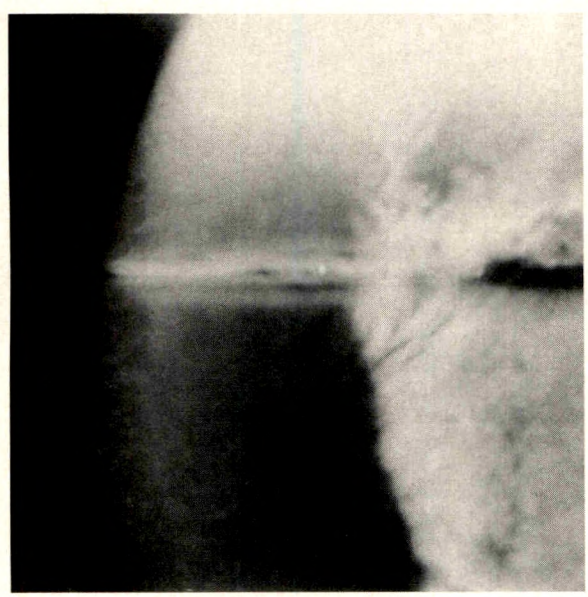


Fig. 4 (Seiler and associates). Patient 1. Excimer laser T-excision on postoperative day 3. Reepithelialization of the edges is already detectable, but the margins of the cut are still irregular.

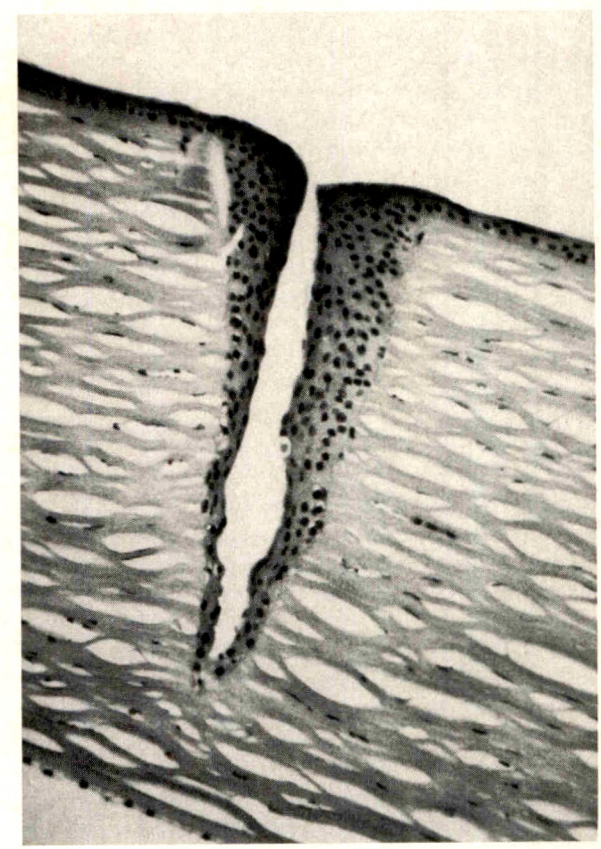


Fig. 5 (Seiler and associates). Light micrograph of an excision in human cornea on postoperative day 4. The epithelium already covers the surface of the excision, but has not yet filled the entire trough.

requiring a minimal excision depth (less than 50 μm) for an adequate optical effect.

We have used the former method in which linear corneal excisions alter the curvature and therefore induce or change astigmatism. The problem of intraoperative motion artifact is minimized by the use of a contact lens mask that moves with the eye within the field of irradiation. This mask also protects the adjacent tissue from reflected and scattered ultraviolet light.

A primary problem in refractive corneal surgery is the reproducibility of the results and, therefore, the predictability of the outcome. Although incision depth seems to be one of the most critical factors, a steel or diamond knife usually produces significant deviations from the intended depth.[4,9,10] In the excimer laser keratectomies performed in this study, there was close correlation between the intended and the verified excision depth. The measurement from slit-lamp micrography correlated with the intended depth with an error of ±8%.

In our initial excisions we found greater deviation of excision depth than predicted. We discovered that this was related to the tear film in the region of ablation, and found that predictability of desired ablation depth was improved when the tear film was minimized. To control the capillary forces in the gap between the cornea and the contact lens, we created grooves in the posterior surface of the contact lens mask surrounding and parallel to the slits. The excision depth correlates in a linear fashion to the total number of laser pulses.[11] There is, however, a difference in the ablation depth obtained in the corneal epithelium and the stroma. The ablation depth obtained per pulse in the epithelium is approximately twice that obtained in the stroma. With this information, the surgeon can determine the number of pulses necessary to ablate a given depth of corneal epithelium and stroma at a given fluence. The calculated number of pulses needed for the desired depth is entered into the laser microprocessor.

A principal goal of this project was to test the validity of the T-incision theory,[3] a biomechanical model that takes into account a stress-strain analysis of the cornea and the changes caused by T-incisions. This theory predicts a strong dependence of astigmatic changes on incision depth (Fig. 6). Thus, we must compare the total astigmatic effect found experimentally to that predicted theoretically. Figure 6 demonstrates the changes in astigmatism measured as compared to the changes predicted by the model. The clinical data coincide well with the theoretical curve; however, the clinical values are somewhat greater than those predicted.

The greatest difference between the theoretical and the clinical values occurs in the proportion of flattening in the perpendicular meridian to steepening in the parallel meridian. From the biomechanical theory, this proportion of flattening and steepening follows directly from the proportion of transverse strain to longitudinal strain (Poisson's ratio), which leads to a twofold to threefold higher flattening than steepening.[6] However, the clinical data show the proportion to be nearly the opposite of that predicted. This discrepancy is probably the result of our theoretical model not taking into account the influence of those corneal lamellae that do not cross the center, but instead are oriented more parallel to the corneoscleral limbus. The current biomechanical model of the cornea must be refined. The stress enlargement in the untouched layers of the cornea after keratotomy depends linearly on intraocular pressure.[3,12] Since two of the greatest astigmatic changes were detected in eyes with intraocular pressures between 30 and 40 mm Hg (Patients 3 and 5), the altered stress in the cornea may be responsible for the increased effects. Conversely, Patient 10, who also showed an increased

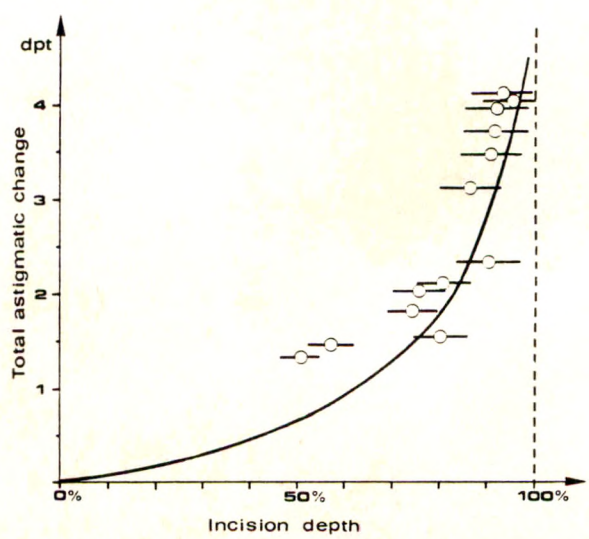


Fig. 6 (Seiler and associates). Total astigmatic changes as a function of excision depth compared with the theoretical curve. The excision depths were determined from slit-lamp photographs; the measurement error was estimated to be ±8%.

effect, had a preoperative and postoperative intraocular pressure of 14 mm Hg.

The temporal course of the refractive effect is different after laser excision than after blade surgery. After blade incisions, a maximal refractive change is found immediately after the incisions, followed by a regression.[13] After laser keratectomy, we found that the maximal refractive effect occurs over one month. The great changes of astigmatism found within the first two postoperative days is probably a result of stromal edema. The differences after these procedures imply that different repair mechanisms are present and should be investigated histologically.

Before concluding a discussion of laser keratectomy, possible side effects and complications of this procedure must be considered. Thermal loading of the tissue adjacent to the excision is important. During ablation, gases expelled from the excision site are found to have temperatures as high as 1,000 K.[14] Experimental investigations[15] have shown that the temperature rise in the stromal tissue depends on fluence and repetition rate of the laser. At the fluence of 165 mJ/cm^2 used in our study, a repetition rate below 50 Hz was adequate to prevent temperature increase to more than 42 C within the adjacent corneal stroma. Indeed, thermal changes in histologic analysis have not been found deeper than 400 nm from the ablation margins.[16]

In addition to thermal loading, the possibility of actinic damage must be considered in association with exposure to 193-nm photons. The epithelial cells are, potentially, at greatest risk. In photoreactivation experiments performed in yeast cells, which are comparable to epithelial cells geometrically, we determined that DNA damage is induced by excimer laser radiation at 193 nm.[17] However, Nuss, Puliafito, and Dehm[18] demonstrated in human epithelial cells that unscheduled DNA synthesis is not significantly influenced by this radiation. Additionally, we did not find any neoplastic changes within the epithelium of human cornea in long-term studies of more than one year. Our only unusual findings were persisting inclusions and a transparent brown tint within the epithelial plug (Fig. 7).

During photoablation, gas is produced and expelled from the excision site at high velocity, which produces mechanical shock waves that could damage the endothelium. Marshall and colleagues[19] found that when the floor of the linear excision was greater than 30 to 40 μm from the endothelium, there were no detectable changes induced in the endothelial cells. From these data, it appears that excisions up to 95% of the corneal thickness can be made without endangering the endothelium.

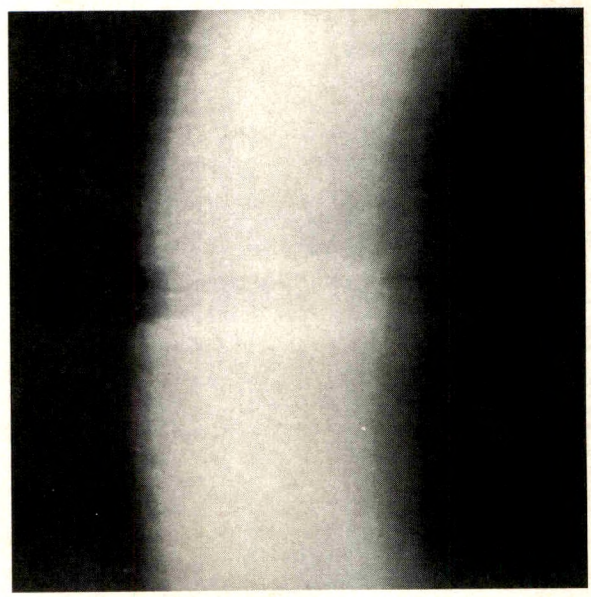


Fig. 7 (Seiler and associates). Excimer laser keratectomy one year postoperatively. The epithelial plug shows small inclusions and a brown tint. Some scarring may be detected at the side walls of the excision.

Corneal laser surgery seems to be an elegant and highly precise procedure. The precise control and uniform depth of the excision leads to improved predictability of the desired refractive result. Various incision shapes can also be preplanned and created that may be more suitable for modifying the corneal topology than the linear and circular incisions currently used.

ACKNOWLEDGMENT

Prof. Dr. H. Witschel, Berlin, performed the histologic processing of one eye (Fig. 5).

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OPHTHALMIC MINIATURE

"Well, she looked at me with her big eyes." Matilda, whose face was slender, had huge eyes, as notable as Uncle's blue ones—monstrously large or as they say, humongous eyes. . . .

"What color are those eyes?" I said. "That crazy Poe says 'hyacinth hair.' Hyacinth is a kind of amethyst or sapphire."

Uncle was pleased with this sign of interest, a preface to acceptance or friendliness, perhaps. "They're lilac color!"

Saul Bellow, *More Die of Heartbreak*
Wm Morrow and Co., 1987, p. 124

Sensorineural Hearing Loss in Patients With Typical Retinitis Pigmentosa

James M. McDonald, Sc.D., David A. Newsome, M.D., and William F. Rintelmann, Ph.D.

We performed detailed audiologic testing in 45 patients with retinitis pigmentosa and 45 age- and sex-matched controls. Ten (22%) of the retinitis pigmentosa patients had a sensorineural hearing loss that varied from mild to severe. None of the control subjects had a hearing loss. Audiograms measured over a ten- to 30-year period were available for four patients with retinitis pigmentosa and each showed progressive hearing loss. The results indicate the important role of audiologic evaluation in treating patients with retinitis pigmentosa.

RETINITIS PIGMENTOSA is characterized, in part, by variably progressive loss of vision and photoreceptor degeneration. The pathophysiologic mechanism of retinitis pigmentosa is unknown. Retinitis pigmentosa has been associated with profound congenital sensorineural hearing loss since the reports of von Graefe in 1858.[1] In 1914 Usher[2] published extensive case reports documenting the coexistence of these two severe sensory handicaps in members of single sibships. Thus, the term Usher's syndrome has been applied to this type of hearing loss found together with clinical manifestations of retinitis pigmentosa. Some investigators believe that Usher's syndrome may be different from typical retinitis pigmentosa.[3-5] The occurrence of a hearing loss not attributable to specific etiologic factors has been reported in a small number of selected patients with typical retinitis pigmentosa, but documentation of ophthalmic disease has been inconsistent.[6-8]

To learn more about the possible coexistence of sensorineural hearing loss in patients with typical retinitis pigmentosa, we investigated the status of the auditory system in both retinitis pigmentosa patients and age- and sex-matched normal controls.

Subjects and Methods

Patients were said to have typical retinitis pigmentosa if they (1) gave a history of progressive loss of vision, (2) showed typical visual field loss by Goldmann perimetry, (3) had an extinguished or nearly extinguished electroretinogram with loss of rod function predominating over loss of cone function, and (4) had a cluster of anatomic findings including narrowed retinal arterioles, vitreous cells, and widespread retinal pigment epithelial changes. The pattern of loss of rod and cone function was determined by two-color threshold discrimination, performed as described by Massof and Finkelstein.[9] Patients were grouped according to degree of rod and cone function: patients with similar degrees of loss of rod and cone function in the spots tested were classified as type I, and those with rod loss predominating over cone loss were classified as type II. The family histories were elicited by detailed questioning and, in many cases, were confirmed by examination of family members. Patients with no family history of retinitis pigmentosa were said to have a simplex-type retinitis pigmentosa. Patients with affected members of the same generation but not in other generations were

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considered to have multiplex or recessive retinitis pigmentosa. Recessive inheritance was diagnosed particularly in patients with a history of consanguinity.

Controls were chosen to match the sex and race of the patients and to be within two years in age. Five of the 41 controls were siblings of retinitis pigmentosa patients, confirmed to be normal by ophthalmologic examination. A thorough otologic history was elicited by using a self-administered questionnaire and a verbal history performed by one of us (J.M.M.). Noise exposure, systemic illness, drug exposure, otologic diseases, and present hearing function were investigated in detail. Any patients with predisposing factors such as noise exposure were excluded, and their hearing was not tested. Two retinitis pigmentosa patients and three potential controls who sought to participate in the study were excluded for either noise exposure or history of acute febrile illness associated with hearing loss in childhood.

Pure-tone air and bone conduction threshold levels were obtained with the Carhart-Jerger modification of the Hughson-Westlake procedure[10] via a clinical audiometer. Air conduction threshold levels were determined at octave frequencies from 250 to 8,000 Hz. Bone conduction threshold levels were obtained at octave intervals from 250 to 4,000 Hz. The audiometer was calibrated periodically according to the American National Standards Institute for normal values for air and bone conduction threshold levels, respectively.[11,12]

Spondee threshold levels and speech recognition scores at 40-dB sensation level were obtained using recorded Central Institute for the Deaf W-1 and W-22 speech stimuli, respectively. Tympanograms were obtained on all subjects.

To determine the presence of a hearing loss, the average pure-tone thresholds in decibels at 500, 1,000, and 2,000 Hz were computed and compared with normal values. For subjects under 26 years of age, the American National Standards Institute (ANSI, 1969) 0-dB hearing level was used as the reference level. For subjects 26 years of age and older, the thresholds were evaluated by sex and age by one of us (W.F.R.) from data collected by Corso.[13] These presbycusic data[13] are thought to represent the best threshold levels obtainable from otologically normal individuals selected at random from a population with history of minimal exposure to potentially damaging noise.

The audiometric configurations we obtained were classified into four types: (1) high frequency, gradual: progressively greater loss for higher frequencies at a slope of 5 to 10 dB per octave for two or more octaves; (2) high frequency, sharp: progressively greater loss for higher frequencies at a slope of greater than 10 dB per octave for two or more octaves; (3) flat: no greater than ±10-dB change per octave across the entire frequency range from 250 to 8,000 Hz; and (4) low frequency, rising: progressively less loss for higher frequencies at a slope of 5 to 10 dB or greater per octave for two or more octaves in the low to middle frequency range.

We assessed test-retest variability under our examination conditions by retesting at random six retinitis pigmentosa patients and three controls. We also performed additional studies on available retinitis pigmentosa patients who had initially shown a hearing loss. These additional studies included: (1) repeated air and bone conduction threshold determinations; (2) speech recognition at a 40-dB sensation level speech reception threshold; (3) middle ear acoustic immitance measurements, including tympanometry, contralateral and ipsilateral acoustic reflex thresholds, and acoustic reflex decay at 500 and 1,000 Hz; (4) masking level differences at 500 Hz; (5) auditory brainstem responses at 80-dB noise hearing level and at 50-dB noise hearing level; (6) short increment sensitivity index at 75-dB hearing threshold level; (7) dichotic digits at 50-dB hearing threshold level; (8) pitch pattern recognition at 50-dB hearing threshold level; and (9) 0% and 60% time-compressed speech at 50-dB hearing threshold level.

Results

A total of 45 retinitis pigmentosa subjects underwent audiologic examination. Two additional persons were tested, but were not considered in this analysis, since they had an atypical form of the retinitis pigmentosa process. Both of these individuals had normal hearing. A similar number of age- and sex-matched normal controls were tested (Table 1). Patients with retinitis pigmentosa ranged in age from 7 to 67 years (average, 36.1 years). The control subjects ranged in age from 7 to 68 years (average, 35.8 years). Both groups contained 42 whites, two blacks, and one native American.

Test-retest reliability was assessed in three

TABLE 1
RETINITIS PIGMENTOSA SUBJECTS CLASSIFIED BY SEX, PATTERN OF INHERITANCE, AND PRESENCE OF SENSORINEURAL HEARING LOSS

	TOTAL GROUP (N = 45)	HEARING LOSS GROUP (N = 10)
	NO. (%)	NO. (%)
Sex		
Male	23 (51)	4 (40)
Female	22 (49)	6 (60)
Dominant	17 (38)	2 (20)
Recessive	3 (7)	2 (20)
X-linked	1 (2)	0 (0)
Simplex	20 (44)	6 (60)
Multiplex	4 (9)	0 (0)

TABLE 2
PATTERNS OF SENSORINEURAL HEARING LOSS IN RETINITIS PIGMENTOSA PATIENTS (N = 10)

PATTERN	NO. BY SEX	(%)
High frequency, gradual	0 M, 1 F	(10)
High frequency, sharp	0 M, 3 F	(30)
Flat	1 M, 1 F	(20)
Low frequency, rising	3 M, 1 F	(40)

control and six retinitis pigmentosa subjects. Their threshold levels for pure-tone stimuli were generally identical, with intervals of one to three months between tests. In no case did the threshold levels obtained vary more than 5 dB at more than one frequency per ear.

Ten retinitis pigmentosa patients (22%) showed some degree of hearing impairment, ranging from mild to severe sensorineural loss. None of the control group subjects showed a significant degree of hearing loss. In our hearing-affected retinitis pigmentosa group, there was a higher percentage of individuals with a recessive or simplex-type family history than in the total group (Table 1). There was also a slight predominance of females in the hearing-affected group as compared with the total retinitis pigmentosa group.

The pattern of hearing loss varied from a low-frequency, rising pattern to a less common high-frequency gradual loss pattern (Table 2). The most frequently observed pattern of hearing loss was a low-frequency-type loss, although this often was accompanied by some degree of high-frequency loss. Four females and no males showed the predominant high-frequency loss pattern (Table 2). Our two youngest patients with sensorineural loss each showed a low-frequency pattern; one also showed a mild high-frequency loss. Except in those individuals with the most severe degrees of hearing loss, the middle frequency levels were relatively spared.

Previous pure-tone threshold data were available for four of our subjects with sensorineural hearing loss. In each case, there appears to have been a slowly progressive loss, again with a suggestion of middle frequency range sparing (Fig. 1). The rate of loss appeared to vary from over 5 to approximately 30 dB per decade. The degree of loss usually was not symmetrical (Fig. 2).

Available subjects who had a sensorineural deficit on initial testing were asked to return, not only for repeat audiometry, but also for additional detailed audiologic examinations. These repeat studies were all consistent with a cochlear site of the lesion. In all but one case, where the auditory-evoked potential was borderline abnormal, these studies were consistent with the theory that the sensorineural hearing loss experienced by our subjects was caused by damage or degeneration within the cochlea.

Discussion

The present study both expands our knowledge of the coexistence of sensorineural hearing loss with retinitis pigmentosa and confirms a previous report[14] of the progressive nature of this hearing loss in at least some patients with retinitis pigmentosa. The degree of hearing loss in our patients varied from mild to severe. The presence of relatively normal speech patterns in those individuals with a severe degree of hearing loss, as well as the documentation of progression from moderate to severe hearing loss in at least one of them, supports the possibility that this is a distinct entity from the profound congenital hearing loss of Usher's syndrome. Persons with severe acquired hearing loss typically have substantially better speech and voice characteristics than individuals with similar degrees of congenital hearing loss. Thus, our findings support the clinical

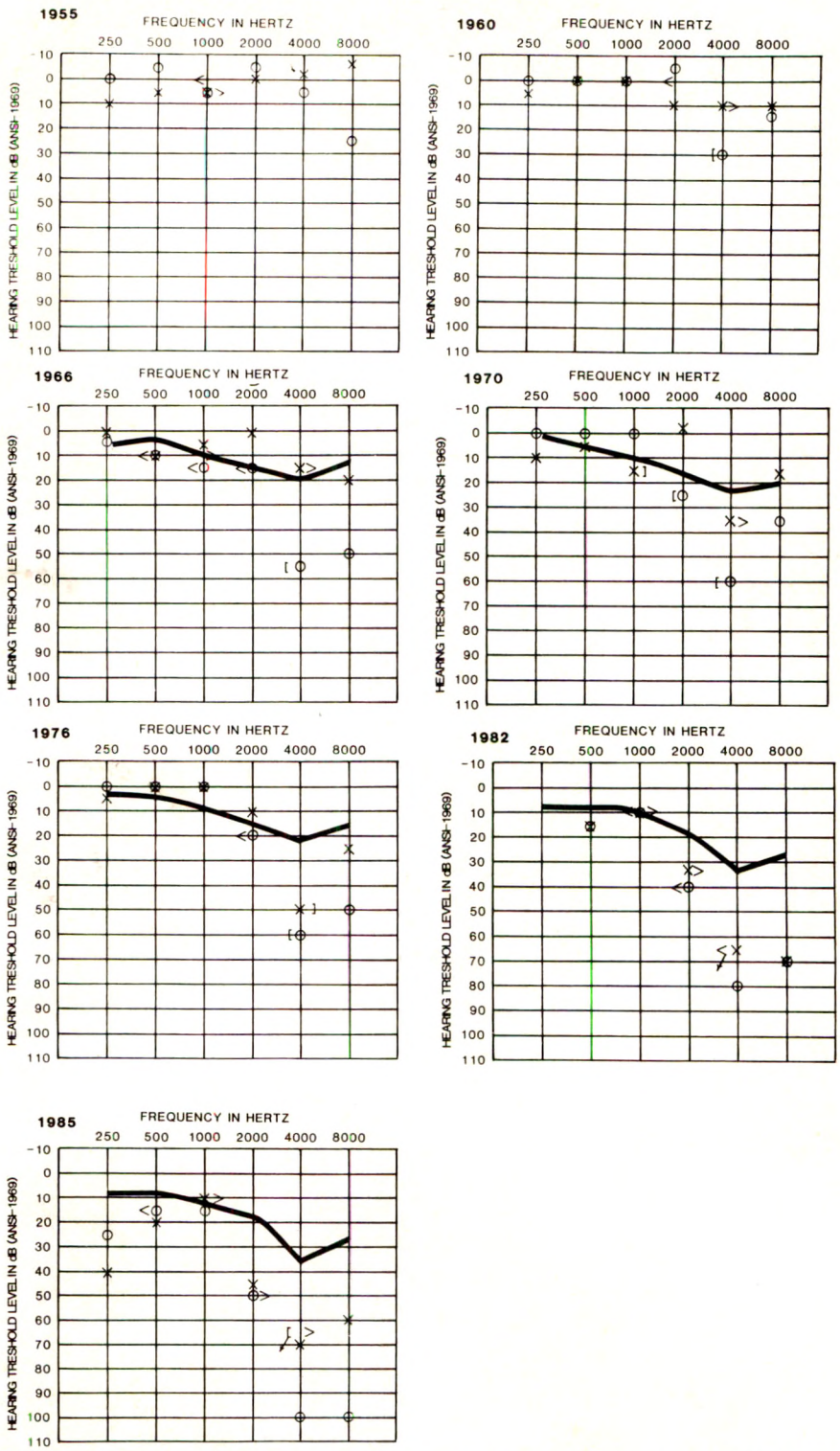


Fig. 1 (McDonald, Newsome, and Rintelmann). Seven pure-tone audiograms over a 30-year period from age 36 to 66 years in a man with retinitis pigmentosa and no family history. Age-adjusted thresholds from Corso[13] are shown as a solid line. ANSI, American National Standards Institute. Pure tone audiograms for air conduction, O = right ear, X = left ear; unmasked bone conduction, < = right, > = left; masked bone conduction, [= right,] = left.

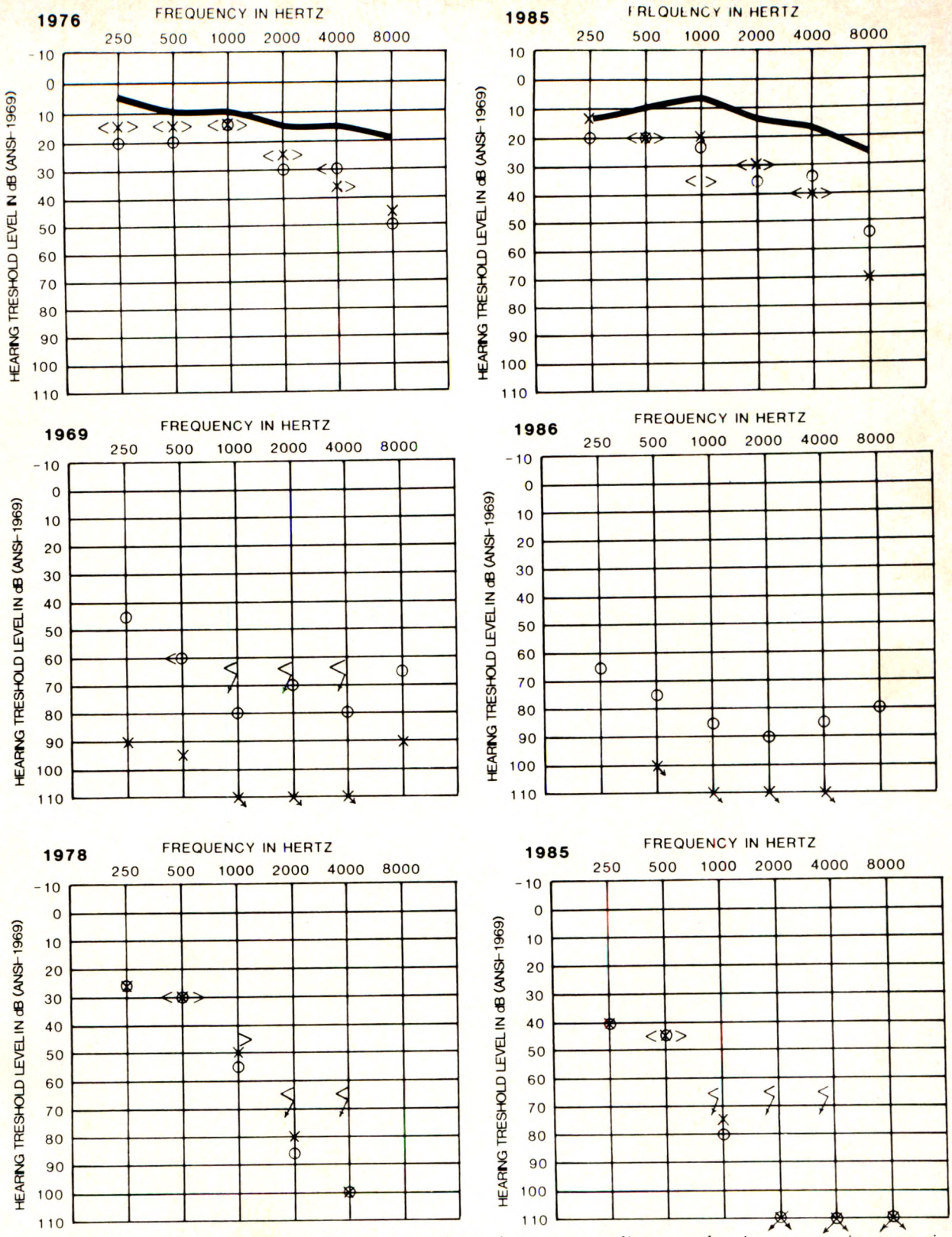


Fig. 2 (McDonald, Newsome, and Rintelmann). Pairs of pure-tone audiograms showing progressive sensorineural hearing loss. Top, From age 52 to 61 years in a woman with retinitis pigmentosa and no family history. Middle, From age 14 to 30 years in a woman with retinitis pigmentosa and a probable recessive family history. Bottom, From age 20 to 27 years in a woman with a recessive family history. Age-adjusted thresholds from Corso.[13] ANSI, American National Standards Institute. Air conduction, O = right ear, X = left ear; unmasked bone conduction, < = right, > = left; masked bone conduction, [= right,] = left; symbols with arrows = not heard.

division between retinitis pigmentosa with associated acquired hearing loss and Usher's syndrome of retinitis pigmentosa and profound congenital deafness. This clinical distinction was not made by Usher, who described 19 of 69 subjects with pigmentary retinopathy and hearing loss as having only "some degree of deafness."[2] The absence of formal audiometry in Usher's study makes comparisons with our study difficult, if not impossible.

Previous studies of smaller groups of patients have shown a sensorineural loss in up to 64% of those studied.[6,15,16] These higher percentages are likely increased because of the inclusion of multiple members from one family, and they do not appear to reflect the true prevalence in a typical retinitis pigmentosa population. The size of our population and that subjects were not recruited for hearing testing per se may also indicate some degree of bias in our study.

We observed some degree of hearing loss in patients with and without a documented family history of retinitis pigmentosa. Most of our subjects with hearing loss had a recessive or noncontributory family history for retinitis pigmentosa, although our numbers are small. Since some patients who showed dominant inheritance also showed sensorineural loss, it appears that the coexistence of eye and ear lesions is not limited to a single genetic type. We did not test multiple family members and thus cannot address the previously reported[6] finding of similar patterns of hearing loss among family members.

The involvement of the two cardinal sensory organs in a progressive degenerative process is not altogether surprising, since the embryologic origin of these organs involves common cellular elements. Structurally, both the hair cells of the cochlea[17] and the photoreceptor cells[18] possess cilium-like structures. Abnormalities in ciliated cells associated with retinitis pigmentosa[19] and in sperm associated with Usher's syndrome[20] have been reported. We chose to use standard descriptive ranges that are related to hearing function to describe hearing status in our subjects. These findings, however, do not tell us about the disease process and may be compatible with a variety of common pathogenetic mechanisms ranging from defects in the genes regulating a particular structural protein to an autoimmune phenomenon.[21]

Our results suggest that clinicians can better serve their patients who are thought to have typical or possible atypical retinitis pigmentosa by determining their hearing status. Complaints of hearing difficulties in young patients with retinitis pigmentosa should be a sufficient indication for formal audiometry. Annual testing could be helpful in determining the progression of any hearing loss. The overall treatment of patients with retinitis pigmentosa who have an associated hearing loss that produces a functional deficit should involve a team approach that can provide specific counseling and training to meet the person's functional needs, particularly in the selection of appropriate amplification and education in methods of improving speech recognition.

ACKNOWLEDGMENT

The two-color scotopic gradients were performed under the direction of Robert Massof, Ph.D., Johns Hopkins University, Baltimore, Maryland.

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OPHTHALMIC MINIATURE

. . . maybe he could go back to Europe, see Paris again, stroll around the battlefields, the ones he remembered, stand there and go back twenty years, hear it again, live again through the shock of men damaging each other, it wasn't killing each other so much, it was the damage they did, the holes they made in each other, the absurd and awesome and unexpected and always horrible wounds, wounds that were so improbable no previous experience could help you, and yet you had to help them, they looked at you, their eyes implored you and you looked at the wound and it was impossible but you had to help them, all the same . . . the fellow who'd come into the aid station that day, his belly bayoneted open—the look of anxiety and wonder on his face, he must have walked a good mile, they were all the same, when they were sick or hurt they all had the look of a child in their eyes, bewildered and humble and expectant—right in his bare hands. . .

. . . Probably dead, now . . . long dead. . .

All but the look. The look lived on. There was something about the look.

Morton Thompson, *Not As A Stranger*
New York, Charles Scribner's Sons, 1954, p. 525

The Relation of Rhodopsin and Scotopic Retinal Sensitivity in Sector Retinitis Pigmentosa

Anne B. Fulton, M.D., and Ronald M. Hansen, Ph.D.

We used reflection retinal densitometric, psychophysical, and electroretinographic techniques to study the scotopic retinal function of a mother and her three daughters who had clinical evidence of a sectoral type of retinitis pigmentosa. Retinal regions with, and those without, ophthalmoscopic signs of degeneration were investigated. During dark adaptation, the time courses of rhodopsin regeneration and recovery of scotopic sensitivity were similar to normal as was the relation of rhodopsin to scotopic threshold. In dark-adapted eyes, threshold increases were not proportional to rhodopsin loss. The results of psychophysical tests of background adaptation and temporal summation, and analysis of the relation of electroretinographic a- to b-wave amplitudes, led to the conclusion that abnormalities of photoreceptor cell function central to the rhodopsin-bearing outer segments accounted for the increased thresholds.

AMONG PATIENTS with retinal degenerative disorders are those in whom ophthalmoscopic signs of retinal degeneration and visual field loss are limited to a sector of retina. Patients with this type of degeneration, sometimes called sector retinitis pigmentosa, often have evidence of autosomal dominant inheritance and only slowly progressive compromise of visual function. Despite the clinical examinations indicating limited areas of involvement of retina, results of recent psychophysical, anatomic, biochemical, and neuropharmacologic studies of sector, or sector-like, retinitis pigmentosa suggest that ophthalmoscopically normal areas of retina are different than normal,[1-4] and that retinal functions other than those occurring in the photoreceptor outer segments are affected.[1-3]

We used reflection retinal densitometric, psychophysical, and electroretinographic techniques to examine the scotopic visual function of a mother and her three daughters, all of whom had clinical evidence of a chorioretinal degeneration resembling sectoral retinitis pigmentosa. Perhaps not surprising in view of the anatomic and biochemical observations,[1-3] our measurements in ophthalmoscopically normal sectors, as well as in abnormal sectors, demonstrated scotopic threshold increases that were not accounted for by rhodopsin loss, and, thus, must be explained by other abnormalities of retinal function.

Patients and Methods

We studied a 44-year-old woman (Patient 1) and her three daughters, aged 22, 20, and 17 years (Patients 2, 3, and 4, respectively), in several sessions over a two-month period. Results of ophthalmoscopic, perimetric, and electroretinographic examinations of Patient 1 had led to the diagnosis of sector retinitis pigmentosa nine years earlier at another hospital. At the time of the initial diagnosis she had no visual complaints, but by age 44 years she was aware of some deficits of visual field and sensitivity in dimly lighted conditions. The daughters had no visual complaints. All patients had a best corrected visual acuity of 20/20 in each eye and clear media.

Each patient had ophthalmoscopic signs of retinal degeneration in the inferior retinas of both eyes; vascular attenuation and bone spicule pigment clumps appeared most advanced in the inferior nasal quadrants. Goldmann perimetry demonstrated areas of field loss corresponding to the ophthalmoscopic abnormalities (Fig. 1).

After the nature and purpose of the electroretinography, reflection densitometry, and

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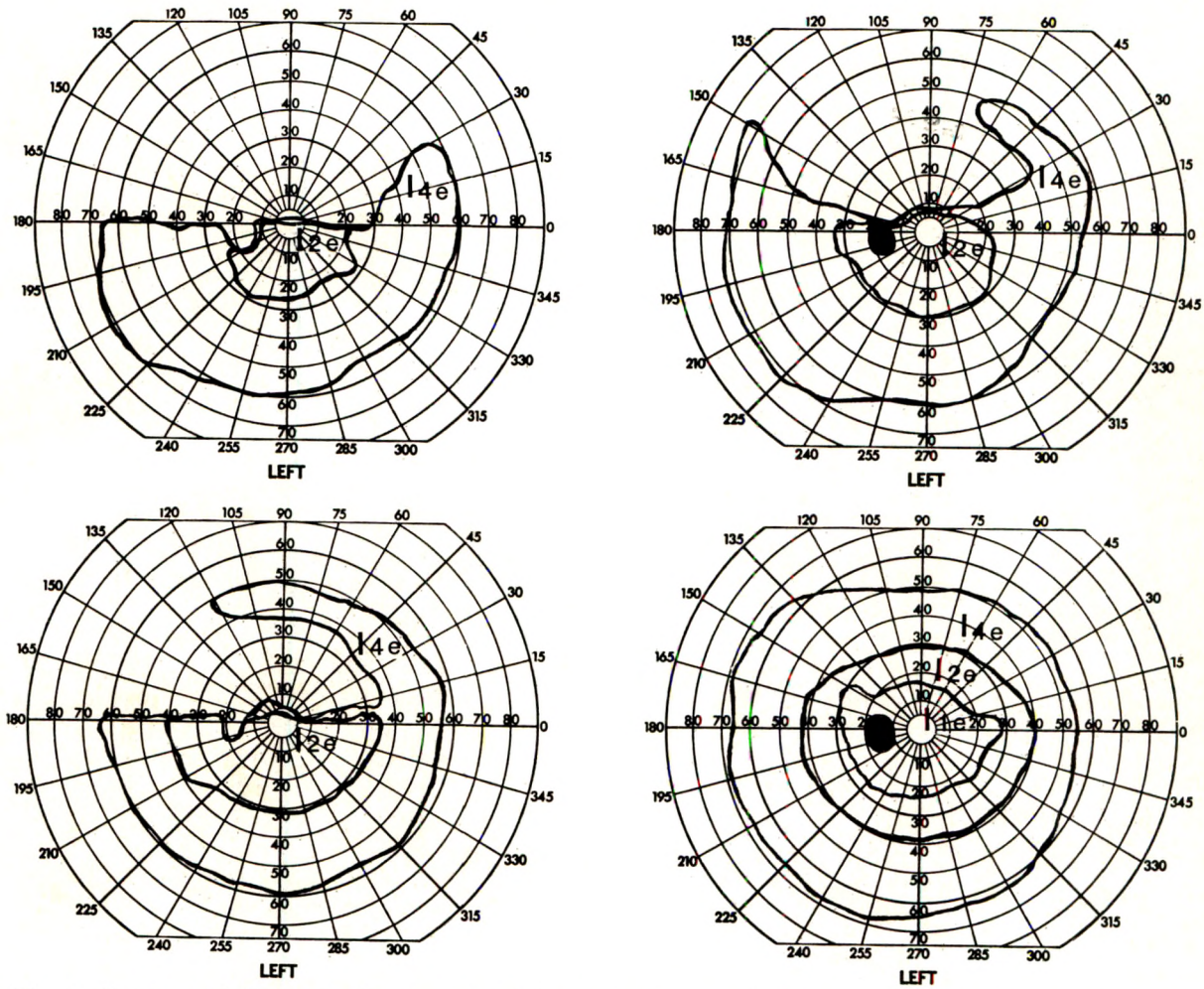


Fig. 1 (Fulton and Hansen). Results of Goldmann perimetry of the patients' left eyes on which the densitometric and psychophysical testing was done. For each patient the areas of field loss correspond approximately to the retinal sectors having narrowed arterioles and bone spicule pigment clumps in the inferior retina. Top left, Patient 1; top right, Patient 2; bottom left, Patient 3; bottom right, Patient 4.

psychophysical measurements were explained, informed consent was obtained. A total of 21 healthy adults, aged 21 to 39 years, with normal eyes participated as control subjects. For the psychophysical and densitometric procedures, left eyes only were tested. Both eyes were tested electroretinographically.

Electroretinography, following previously described procedures[5] that employ full-field, blue ($\lambda < 510$ nm) stimuli, yielded scotopic b-waves with maximum amplitudes attenuated about in proportion to the area of field loss, but with normal implicit times.[6] For each dark-adapted patient the relations of a- to b-wave amplitudes elicited by the blue flashes were examined to evaluate the input of the a-waves, generated by photoreceptors, to second-order retinal neurons, which contribute to the b-wave potential.[7]

The densitometer used was a slightly modified version of the Florida instrument.[8,9] For the present studies, fixation targets were provided that enabled measurements in extra foveal retina. Stray light in the instrument was estimated to be 10% to 20%. The measured two-way density of rhodopsin, which is a fraction of the actual optical density of rhodopsin in the outer segments,[10] was approximated by the ratio of transmissivities of the densitometer wedge settings, $(T_0 - T_D)/T_0$. T_0 is the transmissivity of the fully bleached retina and T_D of the fully dark-adapted retina.[11] This, in effect, gives a measure of the difference in reflectance between the fully dark-adapted and fully bleached fundus.

A measuring light of 560 nm was used to decrease the possible contribution of short wavelength-absorbing photoproducts to the measured density.[11] The measuring light produced about 3.1 log scotopic trolands of retinal illumination that would bleach about 3.3% of rhodopsin if left on indefinitely.[11] In extrafoveal retina, cone cells are not present in sufficient numbers for cone pigments to be assessed by reflection densitometric techniques.

The time courses of rhodopsin regeneration and dark adaptation were studied after two-minute exposures to a 15-degree-diameter spot of white light (6.2 log scotopic trolands) that bleaches >95% of rhodopsin in normal eyes. The sites studied were 18 degrees temporal to the fovea in superior (10 degrees up, clinically unaffected) and inferior (10 degrees down, affected) retina of Patient 3, in the inferior retina of Patient 1, and in the superior retina of Patient 4. Rhodopsin regeneration was measured in a 5-degree spot concentric with the bleached site at various times in the dark after the bleaching light was extinguished until rhodopsin density had returned to the dark-adapted, prebleach value.

Dark-adaptation curves were obtained at the same sites as rhodopsin regeneration measurements were made. A maxwellian view adaptometer was used. Thresholds were determined using the method of limits. The stimuli were white, 20-msec, 2-degree-diameter spots concentric with the 15-degree-diameter bleached site and flashed at 1.3 Hz.

The time courses of rhodopsin regeneration and recovery of log scotopic threshold after bleaching were assumed to be exponential. The time constant of rhodopsin regeneration, τ, was determined by minimizing the root mean square deviation from the relation

$$(T_0 - T) / (T_0 - T_D) = 1 - e^{-t/\tau}$$

where T is the transmissivity of the wedge at any moment. The threshold data were fit by minimizing the root mean square deviation from the relation

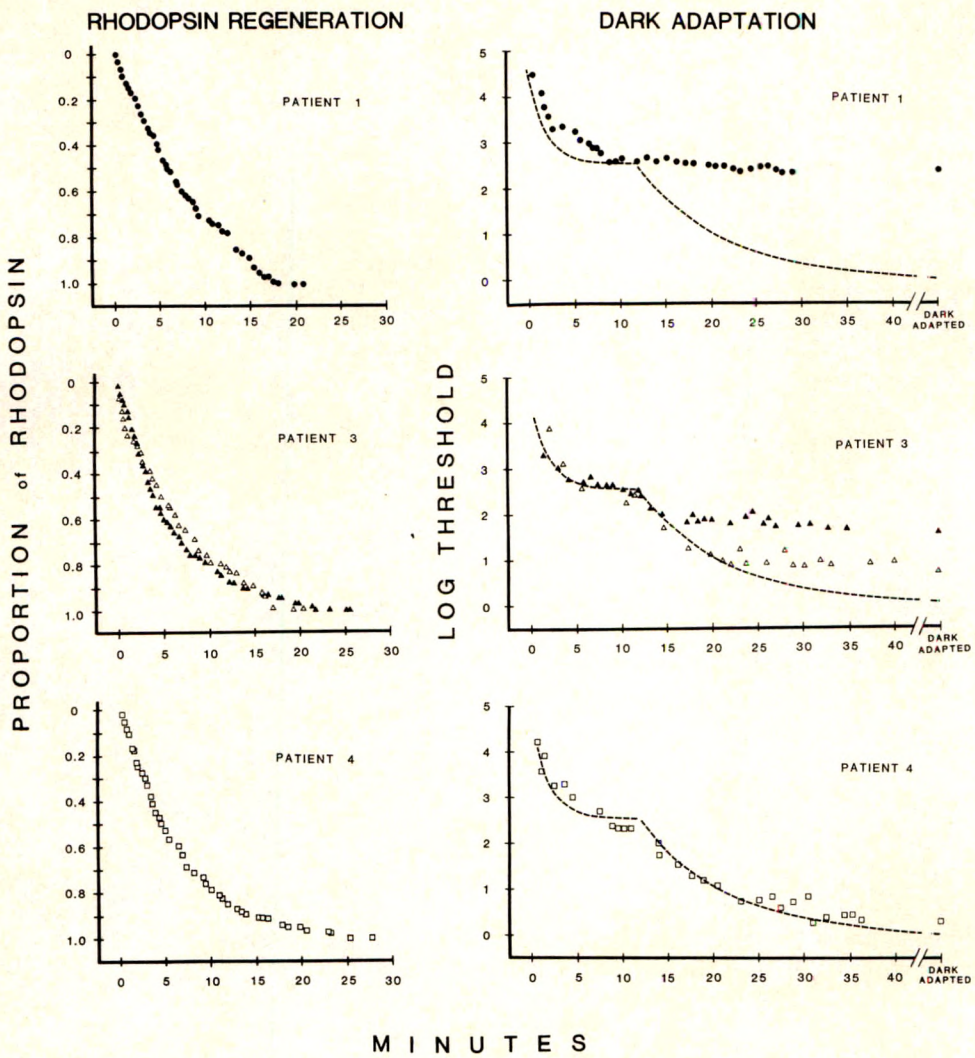
$$\text{Log } I_t = \text{Log } I_D + k e^{-(t - t_{C/R})/\tau}$$

where I_t is the threshold; I_D, the dark-adapted threshold; and $t_{C/R}$, the time of the cone-rod break.

Rhodopsin densities and thresholds were also measured in dark-adapted eyes. Estimates of rhodopsin densities were obtained for Patient 3 and for four normal subjects in a total of ten 2-degree patches temporal to the fovea. In Patient 3, the patches studied included abnormal-appearing inferior and normal-appearing superior retina. In addition, for each dark-adapted patient, five measurements of rhodopsin densities were made in 5-degree patches of retina 18 degrees temporal to the fovea on the horizontal meridian. For seven normal subjects, the highest density was found 18 degrees temporal to the fovea; the mean value was 0.159 (S.D. = 0.006). Herein, we defined a dark-adapted rhodopsin density of 0.159 as 100%. Others have estimated that the average, normal, two-way rhodopsin density is 0.160 (J. Keunen, M.D., D. van Norren, Ph.D., and G. van Meel, M.D., personal communication, September 1986).

Psychophysical thresholds were determined using the method of limits in the same 2- and 5-degree patches of dark-adapted retina in which rhodopsin was measured. With minor modifications,[12] the densitometer was used for these measurements. The stimuli were 100-msec, blue ($\lambda < 510$ nm) spots flashed at 5 Hz. The mean, normal, dark-adapted threshold for the 2-degree spots measured at the retina 18 degrees temporal to the fovea was 4.34 (± 0.46) log equivalent quanta (500 nm)/second/cm^2. Herein all thresholds are expressed relative to this normal mean.

Preliminary inspection of the patients' data showed little if any reduction of rhodopsin density, but substantial increases in dark-adapted thresholds. Adaptation of normal retina to steady, dim, background light causes reductions in retinal sensitivity (increases in thresholds) without bleaching measurable amounts of rhodopsin. Therefore, in background adaptation adjustment of sensitivity depends on processes occurring after absorption of light by rhodopsin in the photoreceptor outer segments, and probably involves retinal cells proximal to the photoreceptors.[13,14] To evaluate these processes in our patients, background adaptation of each patient was investigated. All patients could be tested using a two-alternative, forced-choice, staircase procedure.[15] Adaptation of each patient to a steady, red (10% maximum transmission at 610 nm and 1% at 600 nm), 110-degree diameter background field ranging from −3.0 to +1.0 log scotopic trolands was studied. The stimuli were 1,000-msec, blue ($\lambda < 510$ nm), 10-degree-diameter spots presented 20 degrees to the right or left of the center of the background field. Additionally, background adaptation of Patient 3 was assessed using a maxwellian view optical system, which allowed more precise



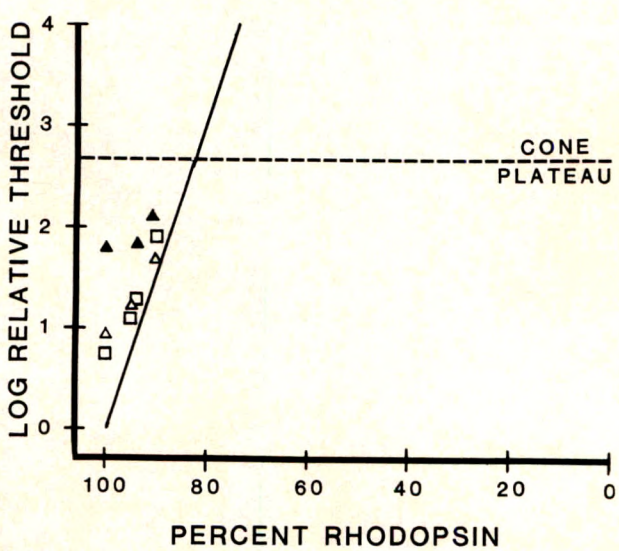


Fig. 2 (Fulton and Hansen). Rhodopsin regeneration and threshold recovery during dark adaptation after >95% bleaches. Upper panel, left, The proportion of rhodopsin present at various times after the bleach. The courses of rhodopsin regeneration for Patients 1, 3, and 4 are similar to normal subjects. Upper panel, right, Log thresholds of Patient 1 (closed circles) and Patient 3 (closed triangles) obtained in ophthalmoscopically abnormal retinal regions, and of Patient 3 (open triangles) and Patient 4 (open squares) obtained in ophthalmoscopically normal regions are shown as a function of time. The dashed curves plot the average, normal course of dark adaptation described in the text. Lower panel, The relation of log relative sensitivity to proportion of rhodopsin present for Patients 3 and 4. Rushton's classic results are represented by the straight line.

control of retinal area stimulated. Test stimuli were 2-degree-diameter, blue ($\lambda < 510$ nm), 20-msec spots flashed at 1.3 Hz, and presented 20 degrees temporal to the fovea. The background was a 15-degree-diameter, steady, red field concentric with the test spot. Thresholds were determined using the method of limits. Psychophysical assessment of temporal summation, a retinal function that can be influenced by processes occurring in postreceptoral cells,[16,17] was evaluated in the dark-adapted retina of Patient 3, 10 degrees temporal to the fovea on the horizontal meridian. The stimuli, presented with the maxwellian view apparatus, were 5-, 20-, 100-, and 1,000-msec, 2-degree-diameter, white spots flashed at 1.3 Hz. Thresholds were determined using the method of limits.

Results

Rhodopsin regeneration and dark-adaptation curves of Patients 1, 3, and 4 are shown in Figure 2. Assuming an exponential course of rhodopsin regeneration, the time constants, τ, were 483 (Patient 1), 420 (Patient 3, superior retina), 356 (Patient 3, inferior retina), and 400 seconds (Patient 4). These values are similar to those obtained from normal controls.[11] Despite the unremarkable course of rhodopsin regeneration, some of the dark-adaptation curves did differ from normal. Although the final threshold of Patient 1 fell below the median cone plateau, there was no definite rod branch. The late thresholds of Patient 3 were increased. The course of dark adaptation for Patient 4 was similar to normal. For normal, naive subjects ($n = 7$) the median time of the cone-rod break was 11 minutes 15 seconds (range, ten to 13 minutes) and the range of recovery of sensitivity after the cone-rod break was 2.8 log units (range, 2.3 to 3.2 log units). Assuming an exponential course of scotopic threshold recovery, the time constants were 460 and 454 seconds for Patient 3 and 545 seconds for Patient 4. For normal subjects ($n = 7$) the median value of τ was 583 seconds (range, 354 to 708 seconds). The rhodopsin regeneration and dark-adaptation curves show that in Patients 3 and 4, as previously reported for nondiseased human retina,[18] at times when rhodopsin has regenerated 90% to 100% of the dark-adapted value, thresholds remain above dark-adapted values (Fig. 2, lower panel). Thus, for these patients, we have no evidence that the relation of rhodopsin to threshold is abnormal during dark adaptation. However, increase of some of the final dark-adapted thresholds motivated further investigation of the rhodopsin-threshold relation in dark-adapted eyes.

TABLE 1
DARK-ADAPTED RHODOPSIN DENSITIES IN 5-DEGREE RETINAL PATCHES, 18 DEGREES TEMPORAL TO THE FOVEA ON THE HORIZONTAL MERIDIAN

SUBJECT NO.	DENSITY
Patient	
1	0.139
2	0.154
3	0.143
4	0.164
Normal subject*	
1	0.156
2	0.168
3	0.168
4	0.157
5	0.157
6	0.151
7	0.155

*Mean ± 1 S.D., 0.159 ± 0.006.

In dark-adapted retina, the rhodopsin two-way densities in 5-degree patches 18 degrees temporal to the fovea on the horizontal meridian were all within the range found in normal subjects (Table 1) except for Patient 1, who had the most advanced disease and only mild reduction of rhodopsin density. The rhodopsin densities at various 2-degree retinal sites in

TABLE 2
RHODOPSIN AND THRESHOLD MEASUREMENTS IN 2-DEGREE PATCHES OF THE DARK-ADAPTED EYE OF PATIENT 3

RETINAL REGION MEASURED			
DEGREES TEMPORAL TO FOVEA	DEGREES FROM HORIZONTAL MERIDIAN	RHODOPSIN TWO-WAY DENSITY, $(T_0 - T_D)/T_0$	LOG RELATIVE THRESHOLD
20	10 down	0.135	1.13
25	10 down	0.127	1.04
30	10 down	0.127	0.76
35	10 down	0.119	0.97
40	10 down	0.115	0.89
20	10 up	0.144	0.21
20	20 up	0.139	0.36
20	0	0.151	0.9
20	20 down	0.125	1.71

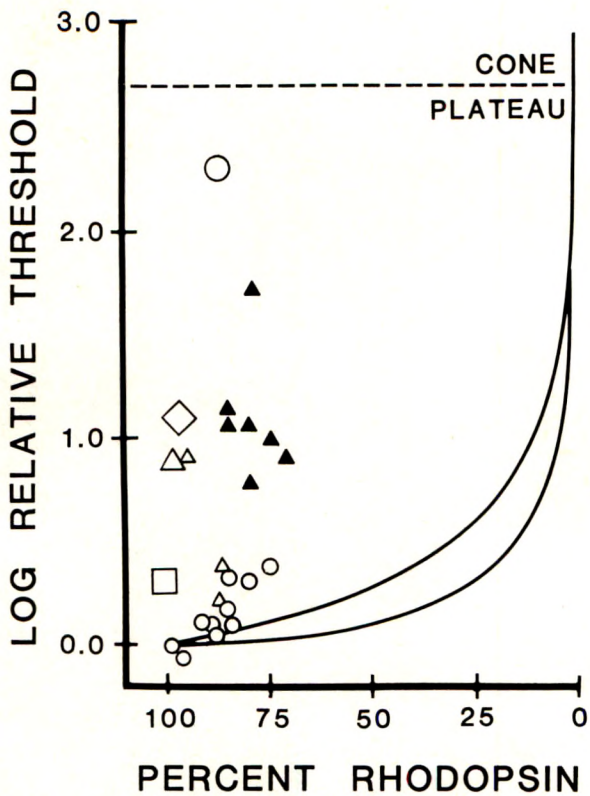


Fig. 3 (Fulton and Hansen). The relation of dark-adapted thresholds and rhodopsin densities. The large open symbols plot the results obtained in 5-degree spots: circle, Patient 1; diamond, Patient 2; triangle, Patient 3; square, Patient 4. The small symbols represent data for the 2-degree spots: filled triangle, Patient 3, ophthalmoscopically abnormal retina; open triangles, Patient 3, ophthalmoscopically normal retina; open circles, mean data of normal subjects (n = 4). The curves plot the quantum catch relation

$$I_t = (1 - e^{-2.3D}) / (1 - e^{-2.3Df})$$

where I_t is the threshold, D is the axial density of an outer segment, and f is the fraction of normal rhodopsin present. Thus, these curves represent relations that would hold if there were an inverse relation of threshold and rhodopsin. The upper curve is for low axial density (0.001); the lower curve is for a high optical density of 1. The median cone plateau of normal subjects (n = 7; see Fig. 2) is shown by the dashed horizontal line.

Patient 3 ranged from 0.151 to 0.115 (Table 2), while the mean densities of normal subjects (n = 4) ranged from 0.159 to 0.118, with standard deviations at each site typically less than 10% (range, 3% to 15%). Thus, the rhodopsin densities in the patients' abnormal- as well as normal-appearing sectors were similar to those found in normal subjects. Thresholds, however, were increased in areas of ophthalmoscopically normal as well as in abnormal-appearing retina. Scotopic threshold increases were not proportional to rhodopsin. Rather, as shown in Figure 3, all of the patients' points lay above the quantum catch locus, the predicted relation if threshold depended directly on the amount of rhodopsin present.

Rhodopsin abnormalities, therefore, do not explain the threshold increases (Figs. 2 and 3). Adaptation to a steady, dim, background, which does not bleach a measurable amount of rhodopsin, did demonstrate some abnormalities of retinal function (Fig. 4). As background intensities increased, the thresholds of Patients 1, 2, and 3 were increased less than those of normal subjects; that is, the slopes of the background adaptation functions for these patients were not as steep as normal. The slope of the function for Patient 4, who had the least advanced disease, was similar to normal.

Because background adaptation can be influenced not only by photoreceptor functions central to the outer segments,[14] but by more proximal retinal cells,[13] psychophysical measures of temporal summation, which depend on postreceptoral function,[16,17] were evaluated and found to be normal (Fig. 5). For the patients, transmission from photoreceptors to second-order neurons,[7] as assessed by the a-wave relation, was also similar to normal (Fig. 6).

Discussion

The patients' results indicate that in the patches of retina surveyed, rhodopsin densities (Tables 1 and 2 and Fig. 3) in the photoreceptor outer segments were normal or only mildly decreased. The normal course of rhodopsin regeneration suggested that the dynamic concatenation of photoreceptor and pigment epithelial processes governing regeneration were normal (Fig. 2). Nevertheless, despite a normal course of recovery of rod dark adaptation in Patients 3 and 4, the final scotopic thresholds of Patient 3 were above normal (Fig. 2). Dark-adapted thresholds at multiple retinal sites of Patient 3 were increased more than would be expected if rhodopsin were the sole determinant of sensitivity (Fig. 3). The mild threshold increases found in ophthalmoscopically normal areas may herald the slow progression that appears to characterize the course of this family's retinal disease. A continuum of severity of functional abnormalities, rather than the demarcation of normal from abnormal

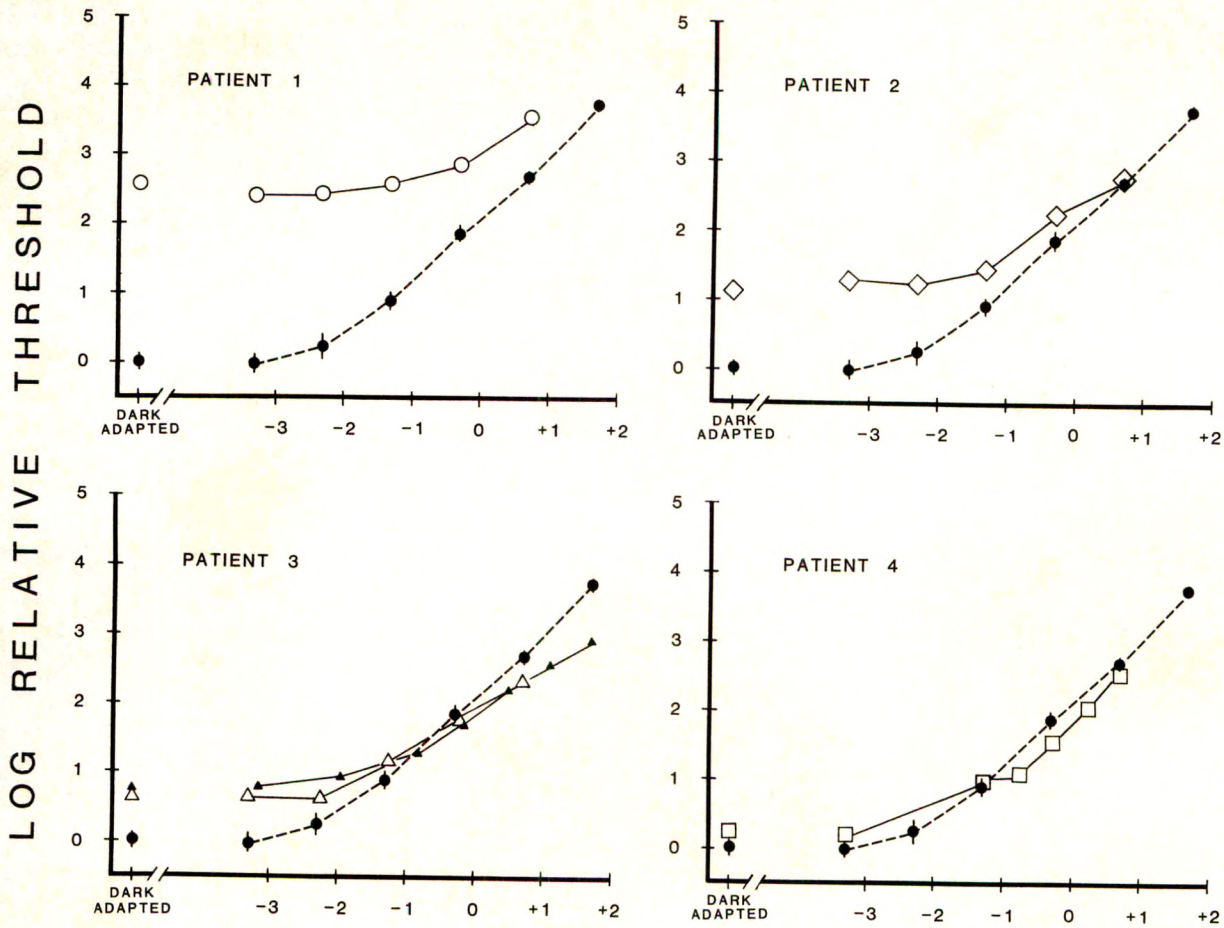


Fig. 4 (Fulton and Hansen). Background adaptation of the patients and normal subjects. The log relative thresholds of dark-adapted eyes and in the presence of various dim red background lights are shown. The open symbols show the patients' results, and the filled circles correspond to the mean ±1 S.D. for normal observers (n = 5) obtained using a two-alternative, forced-choice procedure. The small, filled triangles plot the results obtained from Patient 3 using the maxwellian view apparatus. The slopes of the best-fitting straight lines (method of least squares) through the points obtained with the three most intense backgrounds were as follows: Patient 1, 0.53; Patient 2, 0.63; Patient 3, 0.63; Patient 4, 0.94; normal subjects, range from 0.84 to 0.96 (mean = 0.93, S.D. = 0.05).

retina seen with the ophthalmoscope, is suggested by the group of dark-adapted thresholds of all patients (large symbols in Fig. 3). These thresholds were increased more than expected if sensitivity were dependent only on rhodopsin. In the face of this result, shortening of photoreceptor outer segments or loss of photoreceptor cells appears unlikely to be a fundamental cause of reduced scotopic sensitivity.

While some patients with retinal degenerations have proportional losses of rhodopsin and sensitivity,[19,20] others do not.[20,21] For cooperative patients in whom rhodopsin loss appears to be mild compared to their sensitivity loss, one should be wary of spurious pigment measurements. Rhodopsin measurements by fundus reflection techniques are subject to artifacts introduced by stray light,[10,11] that is, light that has not passed through the visual pigment, but is reflected from the fundus into the photomultiplier tube of the densitometer. If stray light were higher than normal in the patients' eyes, rhodopsin densities would be

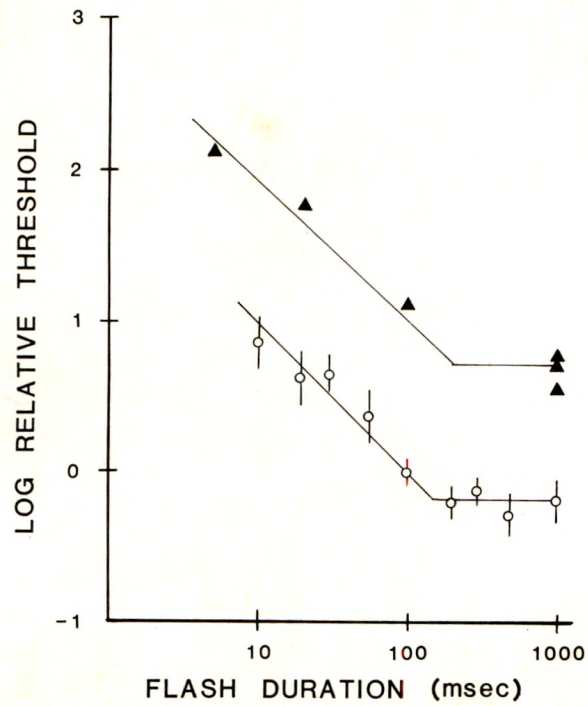


Fig. 5 (Fulton and Hansen). Temporal summation function of Patient 3 (triangles) and a normal subject (circles). Each triangle is the mean of five settings made in one session. Each circle represents the mean data obtained in three sessions. The lines through the data points are drawn by hand. Estimates of the time of complete summation are about 100 msec for both Patient 3 and the normal subject, and are, thus, similar to values previously reported for normal subjects.

overestimated and could lead to the impression that rhodopsin densities were not proportional to loss of retinal sensitivity.

Although we and others have not been able to measure stray light directly in patients, the artifacts introduced by stray light are not thought to account for previous nonquantum catch results.[20,21] Using techniques similar to those used in this study, both rhodopsin loss proportional to sensitivity loss (quantum catch) and modest rhodopsin loss accompanied by marked sensitivity loss (nonquantum catch) have been found in the same laboratory.[20] The severity of the ophthalmoscopically visible lesions did not distinguish the quantum catch from the nonquantum catch patients[20]; therefore, stray light probably did not account for the nonquantum catch result. For patients with choroideremia who have marked fundus lesions that could scatter light, analysis of densitometric data[21,22] indicates that stray light does not account for the nonquantum catch result[21] in choroideremia. In our patients with sectoral ophthalmoscopic signs of retinal degeneration, the fundus abnormalities are less marked than in patients with choroideremia. Although we would hesitate to suggest that fundus appearance is the only predictor of stray light artifacts, it seems even less likely that the nonquantum catch result of the patients with sector retinitis pigmentosa, who have extensive areas of normal-appearing retina, is caused by stray light.

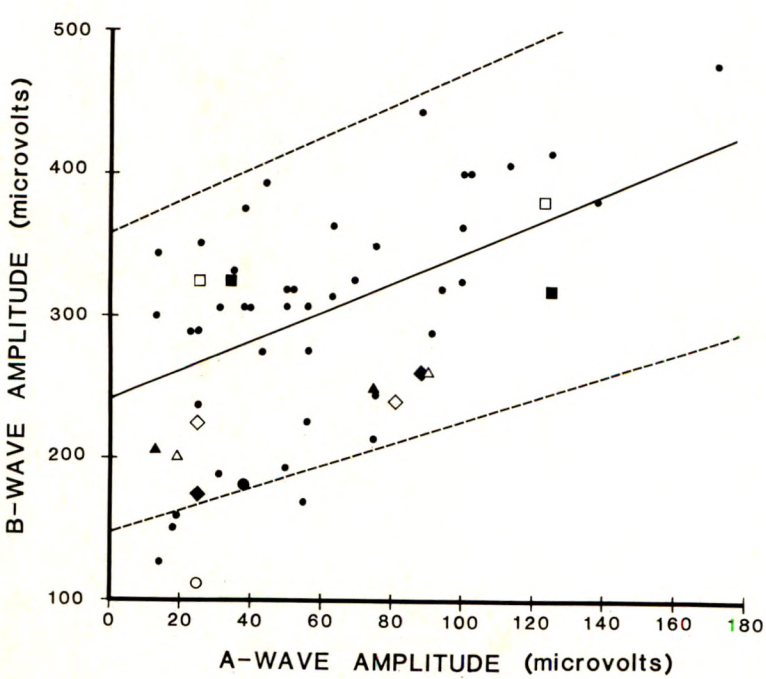


Fig. 6 (Fulton and Hansen). Relation of the a- to b-wave amplitudes. The symbols for the individual patients are the same as in Figures 2 through 4. The filled symbols represent results from right eyes, open symbols from left eyes. The small, filled circles plot the results of normal subjects (n = 5). The solid line is the best-fitting line through data of normal subjects, and the two dashed lines approximate ±2 S.D., thus providing an estimate of the normal range. All but one point of the patients fall within the normal range.

Accordingly, consideration of physiologic explanations for the lack of proportionality between rhodopsin and sensitivity appear to be warranted. Sensitivity is governed by many processes, including those localized in the photoreceptors and in the neural retinal cells proximal to the photoreceptors.[13,14] The normal a- to b-wave relation (Fig. 6) suggests that the transmission of photoreceptors to second-order neurons is not at fault. The normal shape of the temporal summation function (Fig. 5) provides some evidence that postreceptoral function is normal.

Despite the abnormalities in neurotransmitters found in the inner retina of an elderly patient with a chorioretinal degeneration resembling sectoral retinitis pigmentosa,[3] the present results from younger patients lead us to suspect that the deficits in sensitivity are the result of fundamental abnormalities of photoreceptor function that occur subsequent to light absorption by rhodopsin in the rod outer segments. The patients' background adaptation results (Fig. 4) indicate background lights have less effect on sensitivity than normal. Results of other psychophysical tests on patients with X-linked, autosomal recessive and simplex retinitis pigmentosa also show less loss of sensitivity of cone photoreceptors in the light-adapted than dark-adapted state; from these results decreased responsiveness of photoreceptor cells,[23,24] possibly because of cell membrane abnormalities,[25] has been inferred. Perhaps our results indicate that analogous abnormalities in rod photoreceptor cells account for the increased scotopic thresholds.

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Low-Contrast Letter Charts to Detect Subtle Neuropathies

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We performed visual contrast sensitivity testing with Regan's low-contrast letter charts on 30 patients with optic neuropathies and good Snellen visual acuity. Results of this testing were compared with color vision and the presence of an afferent pupillary defect. Regan's low-contrast letter charts were found to be 93% sensitive for detecting subtle optic neuropathies, with the apparent false-negative findings being readily explainable. Color vision testing was abnormal in only 49% of eyes with known optic neuropathies.

Detection of visual contrast sensitivity loss is increasingly important for the early recognition of undiagnosed optic neuropathies. A patient with a subtle optic neuropathy may have normal Snellen (high-contrast) visual acuity, but have visual impairment under low-contrast conditions. Thus, Snellen acuity alone may not detect an optic neuropathy until it is well advanced. Regan and Neima[1] introduced a testing method using charts of variable contrast with Snellen optotypes. Results obtained with these charts are as valid as those obtained with projected sinusoidal grating patterns.[2]

To determine if subtle optic nerve dysfunction is detectable with Regan's charts when Snellen visual acuity is normal, we examined patients with recent and long-standing optic neuropathies of various origins. We compared the results of contrast sensitivity testing to the detection of an afferent pupillary defect and to color vision testing.

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Patients and Methods

We studied 31 patients (35 eyes) with optic neuropathies and a Snellen visual acuity of at least 20/30 in the involved eye. All patients had normal intraocular pressure and no evidence of glaucomatous disk cupping or retinal disease by direct and indirect ophthalmoscopy. Four patients had known bilateral involvement. Each patient underwent testing for projected Snellen acuity, Regan contrast chart testing, color vision evaluation, and testing for an afferent pupillary defect.

Projected Snellen acuity was measured using a mirrored system in a darkened room. The right eye was tested first.

Regan contrast chart testing was performed using two charts. Chart A is a standard Snellen acuity chart with 95% contrast between the darker optotypes and the lighter background (Figure, left). Chart B uses Snellen optotypes but with only a 9% contrast differential between optotypes and background to test visual sensitivity to letters of low contrast (Figure, right). Patients were tested with their best corrected Snellen visual acuity and were asked to read the smallest line possible on each chart, viewed at a distance of ten feet with a luminance of 102 cd/m^2. The right eye was tested first. Each chart has 11 lines with eight letters per line. A subject's response was recorded as the smallest complete line read plus the percentage of correct responses on the next incompletely read line.

Two calculations were made from Chart A and B data: A−B and (A−B) − (A−B). If the patient has a normal chart A value (normal Snellen acuity) and an abnormal chart B value, the visual loss includes a pathway component and is not caused by refractive error. The poorer the low-contrast vision, the larger the A−B value will be. The (A−B) − (A − B) value represents the interocular difference (hereafter

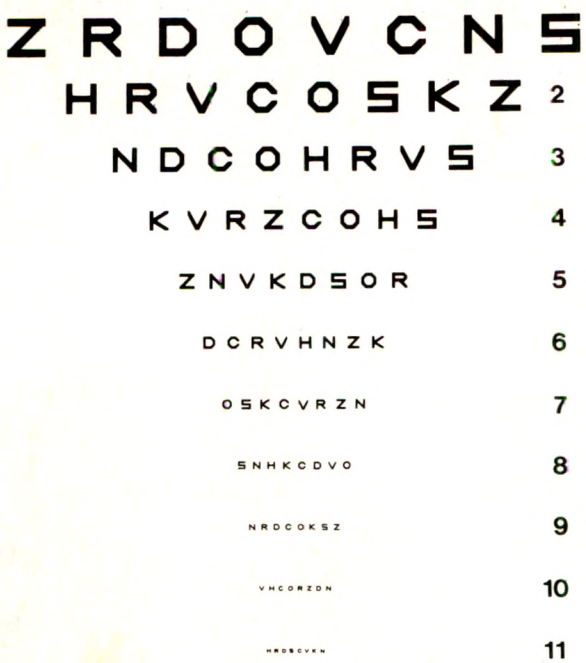


Figure (Drucker and associates). Regan charts. Left, Chart A (95% contrast). Right, Chart B (9% contrast).

designated [A−B]) in pathway transmission between the two eyes and is analogous to the swinging flashlight test.

Normal values (Table 1) were established by testing both eyes of 20 volunteers (11 women and nine men; age range, 23 to 63 years, mean, 34.5 years), with at least 20/20 best corrected Snellen acuity and no history of any visual disorders.

Color vision was tested using standard Ishihara plates read monocularly at 33 cm. Responses were recorded for the right eye first as a fraction of correct readings of the 17 plates, with 1.0 representing a perfect score.

TABLE 1
RESULTS OF LOW-CONTRAST TESTING ON NORMAL CONTROLS
(N = 40 EYES)

SCORES	MEAN	S.D.
A scores	10.06	0.47
B scores	6.60	0.63
A − B values	3.46	0.37
[A − B] values*	0.29	0.26

*[A − B] = (A − B) − (A − B).

Testing for an afferent pupillary defect was performed in a dimly lit room, with the subject fixating on a distant target. Standard techniques were used.[3] The pupillary reactions were graded as negative, trace positive, or positive with respect to the presence of an afferent defect.

The patients included 19 women (21 eyes) and five men (six eyes) with optic neuritis who ranged in age from 14 to 44 years (mean, 28.5 years). Optic neuritis was diagnosed using the clinical criteria of acute visual loss often accompanied by pain on ocular movement or the presence of an afferent pupillary defect. Six of these patients (nine eyes) had multiple sclerosis. Two men (three eyes) (aged 54 and 59 years) had ischemic optic neuropathy as determined by pallid swelling of the optic disk in patients over 50 years of age[4]; one man and one woman (two eyes) (aged 19 and 36 years, respectively) had sarcoid optic neuropathy. The underlying disease was diagnosed by positive results on chest x-ray, gallium scan, or liver or thoracic lymph node biopsy; and three women (three eyes) (aged 21, 41, and 59 years) had compressive optic neuropathies, including two with tuberculum sellae meningiomas and one with a regressed meningioma of pregnancy.

Results

Regan test score results appeared to be unrelated to subject age or sex, as shown by graphic analysis and linear regression. Of 35 eyes with an optic neuropathy, 17 (49%) had a decrease in number of correct responses on the Ishihara color plates.

Twenty-four of the 31 patients had an afferent defect. Of the 24 patients with optic neuritis, 18 (75%) had an afferent defect, five had no afferent defect (two of these five had previously diagnosed bilateral optic neuropathy), and one patient had an equivocal afferent defect and was omitted from all further analyses. Six of seven patients with other optic neuropathies had afferent defects.

The controls and patients were categorized four different ways: (1) by the presence vs absence of known optic nerve dysfunction; (2) by the presence vs absence of an afferent pupillary defect; (3) by the presence vs absence of a color vision defect; and (4) by the presence of an afferent defect or a color vision defect vs absence of an afferent defect and a color vision defect.

Thirty patients had known optic nerve dysfunction, 24 had an afferent defect, 25 had an afferent defect or a color vision defect, and 13 had a color vision defect (12 with and one without an afferent defect).

Student *t*-tests comparing the means of Chart A scores, Chart B scores, minimum B scores, A−B values, maximum A−B values, and [A−B] values for patients with known dysfunction vs subjects without dysfunction were significantly different in all categories at $P < .001$ (Tables 2 and 3).

For each of the Regan chart values we used receiver operator characteristic curves to find cutoff points that optimized sensitivity and specificity for identifying patient eyes with optic neuropathies (Table 4). Chart A scores were poor predictors of optic nerve dysfunction, as no cutoff points optimized sensitivity and specificity at greater than 75%.

When considering a patient's Chart B scores for both eyes, the eye with the lower Chart B score (minimum B) or higher A−B value (maximum A−B) may identify the eye with an optic neuropathy (sensitivity) or identify the more severely affected eye if bilateral dysfunction exists. Similarly, the eye with the higher Chart B score or lower A−B value may identify the eye without an optic neuropathy (specificity).

Using a cutoff point of 5.25 for minimum Chart B scores, 93.3% of patients with diagnosed optic neuropathies and all normal controls were correctly identified (Table 4). Similarly, if a cutoff point of 4.0 was used for A−B values, the same percentages were correctly identified. Thus, minimum Chart B scores or

TABLE 2
REGAN CHART MEAN SCORES*

PROGNOSTIC FACTORS	DEFECT	NO. OF EYES (N = 100)	A VALUE MEAN	A VALUE S.E.	B VALUE MEAN	B VALUE S.E.	A − B VALUE MEAN	A − B VALUE S.E.
Known dysfunction	No	40	10.06	.07	6.60	.1	3.46	.06
	Yes	60	9.49	.11	4.75	.27	4.74	.2
Afferent pupillary defect	No	76	9.93	.06	6.31	.10	3.62	.07
	Yes	24	9.04	.21	2.90	.39	6.14	.28
Afferent or color defect	No	70	9.94	.07	6.39	.11	3.55	.07
	Yes	30	9.19	.18	3.30	.37	5.79	.27
Color defect	No	83	9.82	.07	5.89	.18	3.93	.13
	Yes	17	9.21	.27	3.55	.53	5.66	.37

*$P<.001$ for all scores by *t*-test.

TABLE 3
REGAN CHART MEAN SCORES*

PROGNOSTIC FACTORS	DEFECT	NO. OF PATIENTS (N = 50)	(A − B) VALUE MEAN	(A − B) VALUE S.E.	MAXIMUM A − B VALUE MEAN	MAXIMUM A − B VALUE S.E.	MINIMUM B VALUE MEAN	MINIMUM B VALUE S.E.
Known dysfunction	No	20	0.29	.06	3.61	.06	6.43	.12
	Yes	30	2.09	.25	5.78	.27	3.67	.36
Afferent pupillary defect	No	26	0.31	.05	3.78	.12	6.16	.16
	Yes	24	2.52	.24	6.14	.28	2.90	.39
Afferent or color defect	No	25	0.29	.04	3.69	.08	6.26	.14
	Yes	25	2.46	.24	6.14	.27	2.94	.38
Color defect	No	37	0.97	.19	4.47	.24	5.21	.31
	Yes	13	2.50	.38	6.15	.36	2.83	.55

*$P<.001$ for all scores by *t*-test.

TABLE 4
SENSITIVITY AND SPECIFICITY

PROGNOSTIC FACTORS	VALUE	CUTOFF POINT	SENSITIVITY (%)	SPECIFICITY (%)
Known dysfunction	Maximum A − B	4.0	93.3	100.0
	Minimum B	5.25	93.3	100.0
Afferent pupillary defect	[A − B]	0.875	95.8	96.2
Afferent or color vision defect	Maximum A − B	4.375	92.0	100.0
	Minimum B	5.0	92.0	92.0
	[A − B]	0.875	96.0	100.0

maximum A−B values below 5.25 or above 4.0, respectively, were sensitive enough to identify 93.3% of those patients with dysfunction and specific enough to identify all normal controls without dysfunction. A cutoff point of 0.875 for [A−B] values allowed correct identification of 95.8% of subjects with an afferent pupillary defect and 96.2% of subjects without a defect.

Measurements of current dysfunction, that is, presence of an afferent pupillary defect or a color vision defect, correlated well with Regan chart values. A minimum Chart B score cutoff point of 5.0 identified 92% of patients with an afferent or color vision defect and 92% of those subjects without either an afferent or color vision defect, while a maximum A−B value cutoff point of 4.375 correctly identified 92% and 100% of the same groups, respectively. A cutoff point of 0.875 for [A−B] values was sensitive enough to allow detection of 96% of subjects with an afferent defect or color vision defect and specific enough to detect all subjects without either an afferent or color vision defect.

As expected, there was a poor correlation between Regan chart values and color vision testing. No cutoff points optimized sensitivity and specificity at greater than 80%.

Discussion

Our data indicate that Regan's low-contrast letter charts are able to identify patients with dysfunction (sensitivity) as well as normals without dysfunction (specificity), with a high degree of accuracy. A sensitivity of 93% was obtained in identifying patients with known optic neuropathies with Chart B scores or A−B values. Two patients were not identified by the Regan charts: Patient 6 had a Chart B score clearly within the normal range, a finding that is not readily explainable; and Patient 22 had no afferent or color vision defect and thus, by all measures, had a resolved optic neuritis.

Some patients had Chart B scores and A−B values in the presumably noninvolved eye that were outside of the normal range. Therefore, the Regan contrast sensitivity charts may be a more sensitive indicator of optic nerve dysfunction than our other methods of evaluation.

Visual acuity is measured routinely with high-contrast Snellen acuity optotypes, although visual physiologists have shown that this technique allows various forms of visual dysfunction to escape detection.[5-8] Glaucoma,[9,10] cataracts,[11] various retinal diseases,[12] and optic neuropathies[13,14] may show decreased discrimination of low-contrast objects, while the detection of high-contrast optotypes is relatively spared.

Several different methods have been developed to measure visual contrast sensitivity. Sinusoidal grating patterns illuminated on an oscilloscope present an alternating pattern of light and dark bars of varying contrast and frequency to the viewer. This method may be financially impractical in the clinical setting because of the machinery required. Arden and Jacobson[15] introduced a less expensive method of contrast sensitivity testing that relies on the patient's subjective response to slowly exposed printed sinusoidal grating patterns. More recently, a chart of calibrated variable-contrast sine-wave gratings, each having a different orientation, has been introduced.[16] Regan was the first to combine standard Snellen optotypes and contrast sensitivity.

With all methods of contrast sensitivity testing, high-frequency loss is associated with refractive errors, cataracts, and macular edema; middle-frequency loss suggests glaucoma, cataracts, and optic neuropathies; and low-frequency loss is characteristic of visual cortical anomalies. Loss of contrast sensitivity may depend on the orientation of the grating test pattern.[17] Because of the design of the optotypes, the low-contrast letter charts used in this study are also orientation sensitive.[18]

Color vision assessment is said to be highly selective in the detection of optic nerve dys-

function.[19] However, Wybar,[20] Griffin and Wray,[21] and Perkin and Rose[22] have all reported that only 50% to 68% of the patients with resolved optic neuritis demonstrate color vision abnormalities. This is comparable with our data, which show only 49% of the affected eyes as having abnormal color vision.

The afferent pupillary defect is one of the few objective indicators of unilateral or asymmetric optic nerve dysfunction. One major disadvantage of this test is the necessity for good examination techniques to avoid overlooking minor defects with subtle neuropathies. Additionally, patients with bilateral, symmetric disease will not demonstrate an afferent pupillary defect.

Contrast sensitivity testing has definite advantages compared with other testing modalities. An afferent pupillary defect cannot be detected in the presence of bilateral symmetric optic nerve disease or in monocular patients. The Regan charts demonstrate conduction defects in individual eyes as well as considering the interocular relationship, so that symmetric optic neuropathies are readily detectable.

We believe that the low-contrast letter charts are useful in examining all patients with suspected optic neuropathies because the sensitivity and specificity for detection of optic neuropathy are high, the test is inexpensive, the test demands a verifiable forced choice by the patient (unlike pattern recognition techniques), the testing time is short, the test can be administered by paramedical personnel, and the optotypes are readily recognizable by the patient so that no prolonged explanation or test learning is required.

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Ganglioglioma of the Optic Nerve

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We examined a 15-year-old boy who had a ganglioglioma involving the left optic nerve, which caused proptosis, decreased vision, and optic atrophy. Computed tomography demonstrated an intraconal mass along the course of the orbital portion of the optic nerve. The only evidence of systemic neurofibromatosis was axillary freckling. The patient underwent a combined medial and lateral orbitotomy and excision of the tumor. Histologic examination demonstrated a mass composed of neurons and glial cells characteristic of ganglioglioma. After a one-year follow-up period, we have found no evidence of recurrence.

GANGLIOGLIOMAS are rare, central nervous system tumors composed of a mixture of mature ganglion cells and glial cell elements. We are aware of only one case in which this tumor involved the orbital portion of the optic nerve.[1] We studied a case involving the optic nerve in a patient who might have neurofibromatosis.

Case Report

A 15-year-old boy had proptosis and decreased vision in his left eye. While washing his face and covering the right eye, he discovered he was blind in the left eye. Upon examination, visual acuity was R.E.: 20/20 and L.E.: light perception. There was a left afferent pupillary defect and left optic nerve atrophy. Exophthalmometry disclosed 7 mm of axial proptosis of the left eye. Results of a general physical examination were unremarkable except for axillary freckling. No other signs of neurofibromatosis were present, and there was no family history of neurofibromatosis. Computed tomography of the left orbit demonstrated a large retrobulbar mass, which filled the muscle cone and caused proptosis and flattening of the posterior aspect of the globe (Fig. 1). The computed tomographic scan showed no evidence of intracranial extension or bone erosion. We made a clinical diagnosis of optic nerve glioma. Because of the patient's marked proptosis and poor visual acuity, the optic nerve tumor was removed through a combined medial and lateral orbitotomy (Fig. 2). One year later, the palpebral fissures were symmetrical, and he had full extraocular muscle movements.

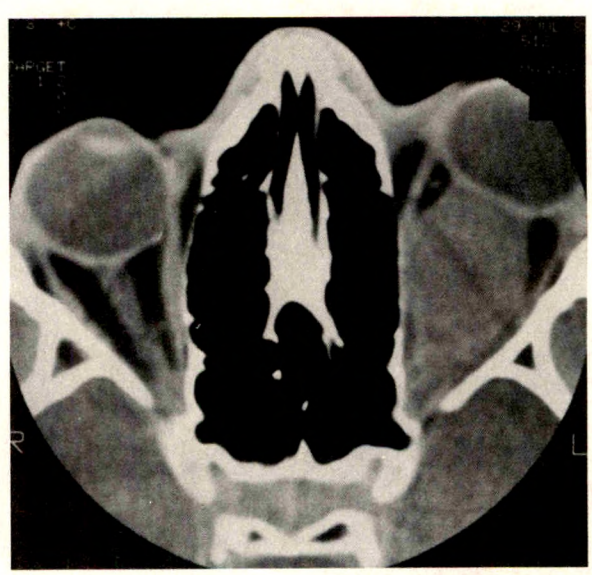


Fig. 1 (Bergin and associates). Axial computed tomography of the orbits showing a large intraconal mass indenting the globe.

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The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the U.S. Government.

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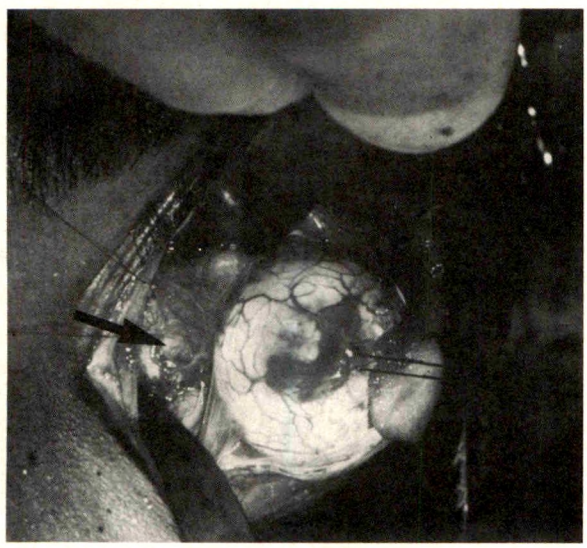


Fig. 2 (Bergin and associates). Intraoperative photograph showing suture inserted through medial rectus muscle insertion to retract globe laterally. Arrow depicts large optic nerve tumor.

Repeat orbital computed tomography showed no evidence of recurrent tumor.

Gross examination of the specimen showed an encapsulated, ovoid mass, which measured 3.0 × 1.8 × 1.5 cm. The capsule was light gray, thin, and had prominent vascular markings. The mass was cut both longitudinally and in cross section. The cut surface had a brown-gray, homogenous appearance.

Microscopic examination demonstrated segments of optic nerve cut in cross section and longitudinally. The normal nerve tissue had been largely replaced by tumor, which was composed of a mixture of proliferating pilocytic astrocytes and large ganglion cells (Fig. 3). The latter stained positive for intracytoplasmic Nissl substance (Fig. 3). Many degenerating ganglion cells were also observed. Several ganglion cells exhibited eccentric nuclei with prominent nucleoli (Fig. 4). Axons were outlined in Bodian-stained sections (Fig. 5). Some areas of the tumor were predominantly composed of fibrillary astrocytes with few ganglion cells. An immunoperoxidase stain for glial fibrillary acidic protein was positive in the astrocytic areas. No mitotic figures or neuroblastic elements were seen. The meninges were markedly thickened and contained a few psammoma bodies. Tumor cells were seen at the posterior cut end of the specimen.

Discussion

Ganglion cell tumors occur more commonly in the peripheral than in the central nervous

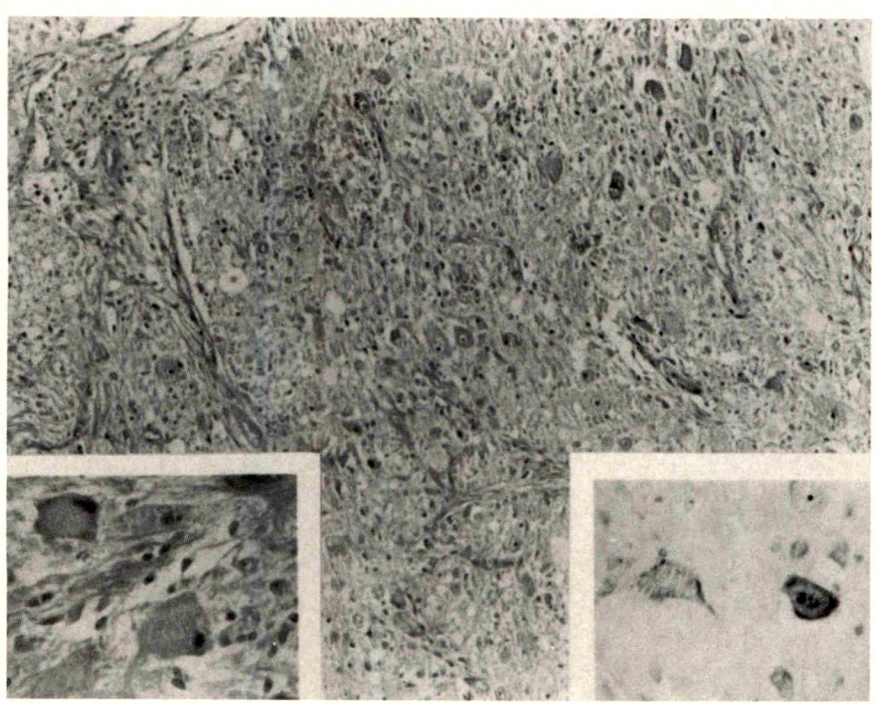


Fig. 3 (Bergin and associates). Main figure, Normal architecture of optic nerve is replaced by a mixture of proliferating pilocytic astrocytes and large ganglion cells (hematoxylin and eosin, ×64). Left inset, Large ganglion cells (hematoxylin, ×160). Right inset, Intracytoplasmic Nissl substance in ganglion cell (cresyl violet, ×160).

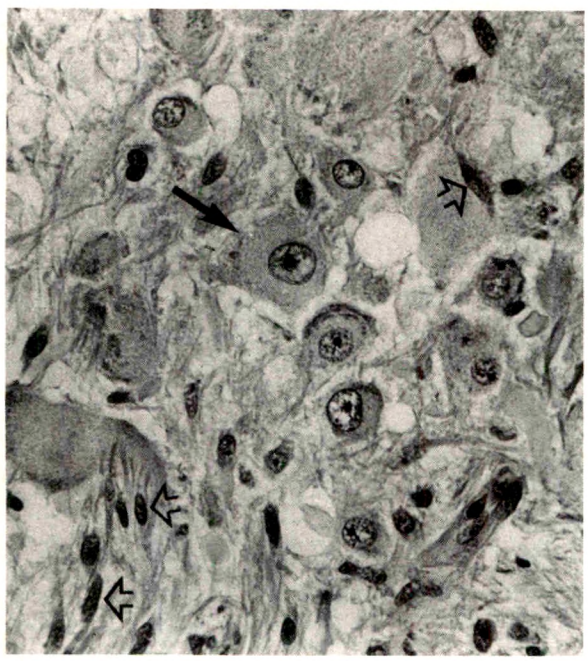


Fig. 4 (Bergin and associates). Section of optic nerve tumor exhibits ganglion cells (closed arrow) in addition to fibrillary astrocytes (open arrows) (hematoxylin and eosin, ×60).

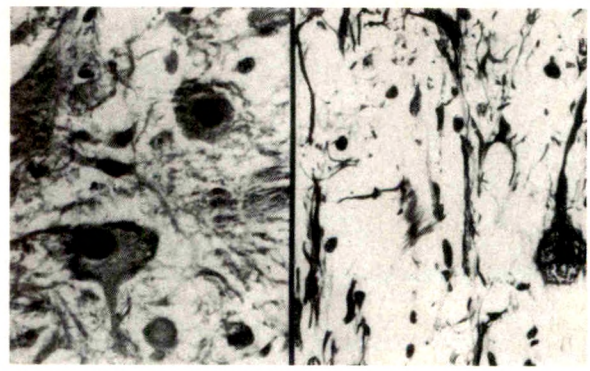


Fig. 5 (Bergin and associates). Left, Ganglion cell (hematoxylin and eosin, ×160). Right, Axons of ganglion cells (Bodian, ×160).

system. They contain nerve cells in various stages of differentiation as well as connective tissue elements. In the peripheral nervous system, the latter are Schwann cells, whereas in the central nervous system, they are primarily astrocytic glial cell elements.[2] Ganglion cell tumors have been subclassified as either gangliogliomas or ganglioneuromas, according to their major component cells. Gangliogliomas, a term coined by Courville[3] in 1930, in the central nervous system consist of a mixture of ganglion cells usually dominated by neoplastic astrocytic cells. Ganglioneuromas of the central nervous system also contain ganglion cells, but the neuronal component overshadows the minimal glial component. In the peripheral nervous system, ganglioneuromas usually originate in autonomic nervous system ganglions.[4] The prevalence of the two cell components of gangliogliomas vary greatly from case to case and even within the same lesion, and make it difficult to distinguish gangliogliomas from ganglioneuromas.

The microscopic appearance of ganglioglioma varies according to the extent to which neuronal and glial cell components are present. The ganglion cells are randomly oriented and may vary in size. These cells may be binucleated, and their nuclei may be eccentrically located in the cytoplasm. The nuclei are usually vesiculated and contain prominent nucleoli. These nuclear characteristics may also be seen in reactive hyperplastic or neoplastic astrocytes. The identification of Nissl substance (cresyl violet stain) aids in this differentiation. Also useful are Bielschowsky's method for staining neurofibrils and Bodian's stain for axons.

The glial cell component of gangliogliomas usually consists of proliferating fibrillary astrocytes. Mitotic figures are rarely seen and the cytologic features of these cells are almost always benign.[2] Malignant transformation rarely occurs.[2]

Gangliogliomas of the central nervous system occur most frequently in children and young adults, and 60% of the patients are under 30 years of age.[2] The most common sites of occurrence are the floor of the third ventricle and the hypothalamus. These tumors are small, firm, and well circumscribed; they are extremely slow growing and cause symptoms compatible with their slow growth in the ventricle and hypothalamus.

One other ganglioglioma involving only the orbital portion of the optic nerve has been reported. Gritzman, Snyckers, and Proctor[1] described a 2-year-old boy who had strabismus and blindness of the left eye. Computed tomography demonstrated diffuse thickening of the orbital portion of the optic nerve, which was excised. Pathologic findings included fibrillary astrocytes as well as ganglion cells. No mention was made of long-term follow-up.

Cogan, Poppen, and Hicks[5] described a 10-

year-old girl who had a ganglioneuroma involving the right intracranial optic nerve as well as the chiasm. She had progressive loss of vision and was treated with excisional biopsy of part of the right optic nerve and with postoperative radiation. Histologic examination showed typical ganglion cells, mature glial cells, and a connective tissue and reticular matrix. There was no recurrence noted after four years.

The pathogenesis of optic nerve ganglion-cell-containing tumors is unclear. Since the optic nerve contains no sympathetic ganglia or neuronal cell bodies, the ganglioglioma may represent a neoplastic proliferation of ectopic neural tissue. Cogan, Poppen, and Hicks[5] postulated that the growth could have arisen aberrantly during early development from autonomic nerves or ganglia along the intracranial vessels. Other theories of the pathogenesis of ganglioglioma of the optic nerve include derivation from more primitive neuroblastic forms, since normal adult neurons do not exhibit proliferative capacity.[1] Dhermy and associates[6] reported a ganglioneuroblastoma of the orbit within neurofibromatous tissue. This tumor contained a mixture of cells, ranging from primitive neuroblasts to well-differentiated ganglion cells.

Our patient had axillary freckling, which has been described as an early sign of neurofibromatosis.[7] He has not developed other signs of neurofibromatosis in the one year since his orbital surgery. Neurofibromatosis was not mentioned as an associated finding in either of the previously reported cases of optic nerve ganglion-cell-containing tumors; however, the relationship of optic nerve glioma and neurofibromatosis is well known.[7-9]

We expect a favorable prognosis for our patient. Typically, benign central nervous system gangliogliomas have the same slow growth characteristics of pilocytic astrocytomas. When astrocytomas are limited to the orbit, the prognosis for life is excellent.[10] Metastatic spread of malignant gangliogliomas within the central nervous system is rare.[2] Neurofibromatosis may have a protective influence on survival of patients with gliomas of the anterior visual pathway.[11] In our case, surgery was undertaken to control proptosis in the patient's blind eye, as recommended by Hoyt and Baghdassarian[12] for treatment of optic nerve gliomas in children.

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A Double-Masked Comparison of Carteolol and Timolol in Ocular Hypertension

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We performed a double-masked study in which 98 patients with ocular hypertension who had been previously treated with timolol received either timolol 0.25% or carteolol 1%, a beta-blocker with intrinsic sympathomimetic activity. The drugs were administered topically twice daily for one month after a one-week washout period. Intraocular pressure was measured at baseline and after one and four weeks of treatment. The appearance of the fundus, external eye, visual fields, tear secretion, blood pressure, and pulse were recorded. Adverse symptoms were elicited using a menu-type questionnaire and an overall judgment of therapy was recorded. Carteolol was as effective as timolol in reducing intraocular pressure. There were significantly fewer patients reporting adverse events overall (P = .019), and eye irritation specifically (P = .02), in the group treated with carteolol.

BETA-BLOCKERS are differentiated based on their selectivity, presence of partial agonist or intrinsic sympathomimetic activity, alpha-adrenergic blocking activity, potency, membrane-stabilizing activity, and pharmacokinetic characteristics.[1] The effects of particular properties must be demonstrated in controlled clinical trials. The standard by which ophthalmic beta-blockers are judged is timolol maleate. In addition to a beta-blocker's efficacy in decreasing intraocular pressure, other areas of clinical interest include potential for systemic effects, particularly pulmonary and cardiovascular effects, as well as effects on visual field and local tolerance.

Carteolol is a long-acting, nonselective beta-adrenergic blocking agent with intrinsic sympathomimetic activity. It was originally developed as a systemic agent for the treatment of hypertension and cardiovascular disease. Volunteer and pilot studies in patients with glaucoma demonstrated the ocular hypotensive effects of carteolol, with efficacy and duration of action approximately equal to that of timolol.[2] A double-masked, multicenter trial comparing carteolol and timolol in Japanese patients with ocular hypertension confirmed equivalent efficacy and less local discomfort or symptoms of irritation in the group treated with carteolol.[3] Carteolol also caused less ocular irritation than timolol in a double-masked study in 36 European volunteers.[4,5] We undertook this study to confirm the efficacy of carteolol as compared to timolol and examine tolerance levels in a European patient population.

Subjects and Methods

Patients were enrolled in this study from the outpatient practices of 11 ophthalmologists in the Frankfurt-Wuerzburg area of West Germany. The study group was supervised by one of us (G.K.K.). All patients had ocular hypertension with or without visual field defects and were either newly diagnosed and untreated or were being treated with timolol alone. Intraocular pressure of patients not yet treated was at least 22 mm Hg on two occasions separated by one week. The intraocular pressure of patients receiving timolol was between 16 and 24 mm Hg, both during treatment and after a one-week washout period. Patients were excluded

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who were receiving antiglaucoma medications other than timolol, who had received any systemic beta-blocker during the previous month, or who were receiving tricyclic antidepressants or monoamine oxidase inhibitors. Patients were excluded who had asthma or recurrent respiratory illness, second- or third-degree heart block, previous myocardial infarct, heart failure, resting pulse rate less than 55 or more than 90 beats/minute, peripheral vascular disease, ocular infections, recent corneal trauma, or intraocular surgery within the last six months. Patients with secondary or closed-angle glaucoma were excluded, as well as those with contact or intraocular lenses, diabetic or progressive retinopathy, or well-defined cataracts.

All patients meeting the eligibility criteria gave informed consent. The study protocol was approved by an ethical review committee formed in accord with United States' regulations governing institutional review boards. Background information on each patient was recorded, including general health status and duration of ocular hypertension.

Intraocular pressure was recorded by applanation tonometry, twice on each eye, in a fixed sequence. Examinations were made of the cornea, and its staining characteristics, and of the conjunctiva, eyelids, optic disk, cup-to-disk ratio, pupil diameter at 31.5 asb illumination, and visual fields, using a Goldmann perimeter. Schirmer testing was performed on an unanesthetized, open eye, and the results were recorded at five minutes. Glaucomatous damage was assessed using the stages cited by Aulhorn[6] and then reevaluated by one of us (G.K.K.) in a masked fashion. Blood pressure and pulse were recorded. Adverse events were systematically elicited using a short menu-type questionnaire, requiring responses as to the presence of headache, eye pain, tiredness, and blurred vision. Investigators and patients recorded an overall evaluation of therapy, using the categories "good," "medium," or "bad." The evaluations were global judgments; the categories were not further defined.

Observations other than perimetry and Schirmer tests were made four times: at the initial screening, after the one-week washout period (the beginning of treatment), and one and four weeks after initiation of treatment. Perimetry and Schirmer tests were performed before and at the end of treatment. Intraocular pressure was generally measured at the same time of day for each patient, 12 or more hours after the last instillation of medication. Washout of prior medication was limited to one week so as to avoid any psychological effects relating to a longer period without treatment. We believed that results five weeks later (after a one-week washout period and four weeks of treatment) would reflect the investigational treatment, not the medication given before the washout period. Studies using a one-week washout period before a one-month treatment period have been used elsewhere in comparative trials of ophthalmic beta-blocking agents.[7,8]

Patients randomly received either timolol 0.25% or carteolol 1%, both of which were packaged in dropper containers identical to those in which timolol is marketed in West Germany. These two concentrations were found equally effective in a previous study.[3] Timolol 0.25% was selected because it is the concentration most commonly used in ophthalmic practice in West Germany. Bottles were labeled with masked, tear-off labels, which were all collected intact at the end of the trial. The assignment of the two test drugs was performed independently for each outpatient practice and for patients who were previously untreated to insure that each patient group would be balanced with respect to study locations and previous treatment. Patients were instructed to instill one drop of the test drug in each eye twice daily, and were required to demonstrate the correct procedure to the investigator at the beginning of the study.

Investigators met for group discussion and training before and during the study.

All data were entered into a database for analysis by two independent operators, with original documents retained for potential verification. In analyzing the values for intraocular pressure, means were examined separately for right and left eyes and for pooled values. Analysis of covariance was used to assess changes between groups adjusted for baseline intraocular pressure. Paired *t*-tests with corresponding confidence interval calculations were used to estimate the magnitude and direction of change in intraocular pressure after initiation of treatment. Within-group comparisons over time were assessed by *t*-tests. The incidences of overall side effects in the two groups were contrasted using chi-square tests; the incidences of specific side effects were contrasted using Fisher's exact test. Blood pressure and pulse measurements were compared using both *t*-tests and Wilcoxon signed-rank tests on original and log-transformed data. Global therapy evaluations were compared using Fisher's

exact test. Pupil diameters and Schirmer test results were compared using both *t*-tests and Wilcoxon signed-rank tests. A two-sided P value of $P \leq .05$ was considered statistically significant.

Data were excluded from analysis if the patient failed to meet the pretreatment intraocular pressure level criteria, was examined one week or more after the day called for in the protocol, or had received treatment with a beta-blocker other than timolol before the study.

Results

Of the 129 patients recruited for the study, data from 116 were used in the analysis (13 patients were excluded from the study). Of these 116 patients, 98 had previously received timolol and 18 had received no treatment for their ocular hypertension. The group of untreated patients was considered too small for statistical comparison. One patient from the timolol group dropped out of the study with complaints seemingly unrelated to treatment (night sweats, nocturia, belching, coated tongue). Therefore, our analysis was based on 97 patients who had previously received timolol. Of these 97 patients, 50 received carteolol 1% and 47 received timolol 0.25%.

Of the 12,994 items of data called for by the protocol for patients suitable for analysis, 12,661 (97.4%) were collected.

The two groups of patients were similar with respect to sex, age, weight, height, intraocular pressure, and concomitant medication. Mean duration of ocular hypertension was 4.1 years in the timolol-treated group and five years in the carteolol-treated group. The groups differed significantly only with respect to responses to a nonspecific question on general health status: 12 timolol patients and two carteolol patients were considered by their physicians to have impaired general health.

After the washout period, patients in both groups experienced a marked increase in intraocular pressure (Fig. 1). After one week of therapy, both groups experienced a marked and statistically significant decrease in intraocular pressure ($P = .0001$ for each group). This decrease was maintained throughout the study period. The group mean intraocular pressures at the end of the study were 19.86 mm Hg and 19.73 mm Hg for the carteolol and timolol

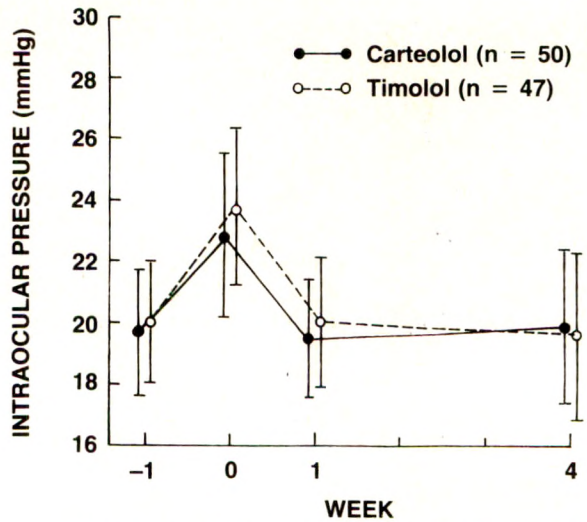


Fig. 1 (Scoville and associates). Effects of carteolol 1% and timolol 0.25% on intraocular pressure in patients with previous timolol treatment for ocular hypertension. Treatment began at week 0 after a one-week washout period. Group means are derived from individual means of four readings of intraocular pressure per patient at each visit. Vertical bars represent standard deviations.

groups, respectively. Analysis of covariance with the baseline intraocular pressure used for adjustment showed no statistically significant differences between the two drugs with respect to effects on intraocular pressure ($P = .92$). The mean change in intraocular pressure from baseline to week 4 of investigational treatment was −0.156 mm Hg for the carteolol group and +0.293 mm Hg for the timolol group. This was not a statistically significant difference ($P = 0.33$). The 95% confidence interval for the difference in mean change between the two groups was −0.474 to +1.375 mm Hg.

Perimetry disclosed no differences between the two patient groups in visual field defects before or after treatment.

Global evaluations of therapy by the investigators and patients yielded judgments of "good," "medium," or "bad." Investigators evaluated therapy as "good" in 40 of 49 patients receiving carteolol at one week and 39 of 50 patients at four weeks. Investigators judged treatment "good" in the timolol group for 30 of 47 patients at one week and 26 of 46 after four weeks. The difference between groups was significant after four weeks of treatment ($P = .07$ at one week and $P = .03$ at four weeks). The patients gave global evaluations favoring carteolol, but the difference did not achieve

statistical significance (P = .07 at one week and P =.32 at four weeks).

Patients reported adverse events or potentially drug-related symptoms after treatment 41 times in the carteolol group and 95 times in the timolol group; this difference was statistically significant (P < .001). The number of patients reporting adverse events was also significantly different between the two groups. Eleven of 50 patients at one week in the carteolol group compared to 24 of 47 patients in the timolol group (P = .03), and 13 of 50 patients at four weeks in the carteolol group compared to 23 of 47 patients in the timolol group (P = .019) reported adverse effects (Fig. 2). Of the four types of symptoms specifically asked about at each visit (eye pain, blurred vision, headache, and tiredness), responses to the question on eye pain showed a statistically significant difference between treatment groups. There were five reports of eye pain during treatment in the carteolol group and 17 reports in the timolol group (P = .02 at four weeks) (Fig. 3). There were fewer reports of headache and tiredness from patients in the carteolol group than from patients in the timolol group. However, the differences between the groups did not achieve statistical significance for headache, tiredness, or blurred vision.

Systolic and diastolic blood pressure as well as pulse rate did not differ significantly between the two treatment groups at any interval.

There were no differences between the groups noted during examination of the external eye (cornea, conjunctivae, eyelids), in pupil diameter, or in the appearance of the optic disk. The cup-to-disk ratio of the two groups did not differ. Schirmer test results did not demonstrate any difference in tear secretion between the two treatment groups.

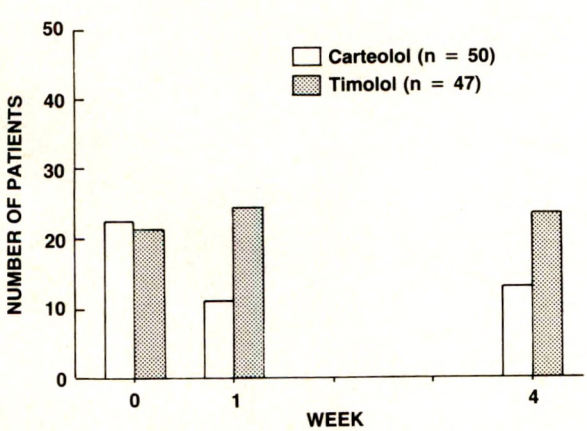


Fig. 2 (Scoville and associates). Numbers of patients reporting symptoms and adverse events after receiving carteolol 1% and timolol 0.25%.

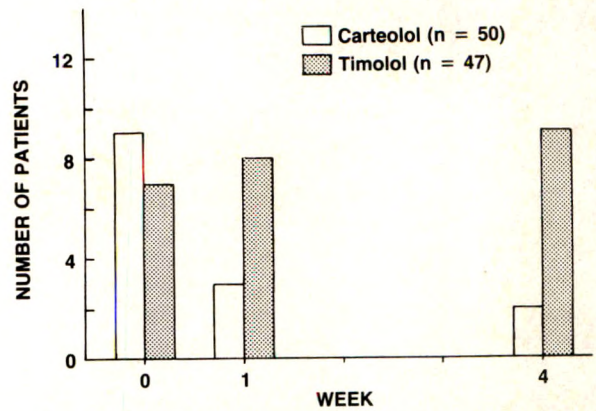


Fig. 3 (Scoville and associates). Numbers of patients reporting eye pain or discomfort after receiving carteolol 1% and timolol 0.25%.

Discussion

Timolol maleate was the first widely used ophthalmic beta-blocking agent. Its efficacy and safety are well established, and it serves as the benchmark against which newer agents are measured. Other beta-blockers have been found at times to be less effective and more uncomfortable than timolol.[7,9] Eye discomfort or stinging have been reported to be frequent with some newer beta-blockers,[6,7] although conflicting results have been reported.[10]

The results of our study show that twice-daily carteolol 1% is as effective as twice-daily timolol 0.25% in lowering intraocular pressure over a four-week treatment period. The inclusion criteria suggest that this study was not biased against timolol, since patients successfully treated with timolol were used. Use of carteolol was associated with significantly fewer reports of eye pain or discomfort than timolol. Investigators gave a global evaluation of good significantly more often under double-masked conditions to the effects of treatment in the patients receiving carteolol than in the patients receiving timolol. This difference in subjective overall judgments is concordant with the difference in reports of adverse events.

There was no difference in cardiovascular effects, although carteolol has previously been shown to induce less bradycardia than timolol.[3] However, all patients in the present study had normal pulse rates, unlike those in the previous study.[3] Patients selected for this study were ambulatory and had achieved fairly good control of intraocular pressure on previous timolol therapy. Thus, they may be considered to suffer from mild to moderate, or nonrefractory, ocular hypertension, with or without visual field defects. This group was selected to be a relatively homogeneous and potentially compliant group. The patients also represent typical, uncomplicated cases of ocular hypertension and glaucoma commonly seen in the outpatient practice of ophthalmology.

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OPHTHALMIC MINIATURE

The table I write on I say exists, that is, I see and feel it; and if I were out of my study I should say it existed—meaning thereby that if I was in my study I might perceive it, or that some other spirit actually does perceive it. There was an odour, that is, it was smelt; there was a sound, that is, it was heard; a colour or figure, and it was perceived by sight or touch. This is all that I can understand by these and the like expressions. For as to what is said of the absolute existence of unthinking things without any relation to their being perceived, that to me is perfectly unintelligible. Their *esse* is *percipi*, nor is it possible they should have any existence out of the minds or thinking things which perceive them.

George Berkeley, *A Treatise Concerning the Principles of Human Knowledge*
London, J. Tanson, 1710

Sustained Reduction of Intraocular Pressure in Humans With the Calcium Channel Blocker Verapamil

Mark B. Abelson, M.D., C. Mitchell Gilbert, M.D., and Lisa M. Smith, B.S.

We investigated the effect of the calcium channel blocker verapamil on intraocular pressure in human volunteers. In the initial trial, 15 subjects with untreated ocular hypertension were tested. After a baseline measurement was obtained with applanation tonometry, a 40-μl drop of verapamil, 1.25 mg/ml, was instilled in one eye. After 30 minutes, a second reading was taken. In a subsequent trial of 12 untreated ocular hypertensive subjects, the duration of action was determined using the same dose and method of delivery. Results showed that verapamil elicited a mean ± S.E.M. change in intraocular pressure of −3.8 ± 0.900 mm Hg in the treated eye, and −1.6 ± 0.400 mm Hg in the untreated eye. This reduction was statistically different in both eyes (treated eye, P = .0007; untreated eye, P = .005). This decrease in intraocular pressure remained statistically significant when compared to predrug baseline values for up to ten hours.

VERAPAMIL was noted to have a minimal but consistent ocular hypotensive activity in normal subjects during routine screening of compounds for a potential mast cell stabilizing activity. The ability of calcium channel blockers to modulate vasculature and other smooth muscles[1] led us to investigate further this effect on intraocular pressure.

Intraocular pressure is maintained as a steady state between aqueous humor formation and aqueous humor outflow. Aqueous humor function has two components that are potentially affected by calcium inhibition: a hydrostatic component from arterial blood pressure and ciliary body tissue pressure, and an osmotic pressure induced by the active secretion of sodium, calcium, and other ions by the ciliary epithelium.[2] In addition to these factors, the outflow of aqueous humor influenced by episcleral venous pressure[2] may be directly affected by calcium inhibition.

Previous studies had shown that oral administration of nitrendipine to humans caused some ocular hypotensive activity, which was attributed to its vascular effects.[3] Conversely, in rabbits and humans, topical administration of various calcium channel blockers was found to increase intraocular pressure.[4]

Because of the diversity of responses found when screening agents for a potential ocular hypotensive effect, it is essential to develop sequentially the spectrum of a drug's effects. First, an agent's activity in animals, regarding both safety and efficacy, should be evaluated. However, because species specificity is commonly observed with ocular hypotensive agents, research should be continued in humans after ocular safety has been assured.

Testing in normal human volunteers, by both oral and topical administration, can uncover a therapeutic effect, yet evaluating a drug in the population in which it would be used is still the most accurate method of pharmacologic screening. Particularly with ocular hypertension, the physiologic disturbance which is responsible, and which remains ill defined, may need to be present in order for the agent to act upon it.

The objective of this study was to determine if topical administration of the calcium channel blocker verapamil had an effect on intraocular pressure in ocular hypertensive humans, and, if so, to determine the duration of this effect. Since the activity of a potential ocular hypotensive agent is often overlooked because of the diurnal variation of intraocular pressure, we compared the effects of verapamil both to the

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predrug baseline pressures and to a natural diurnal curve of intraocular pressure identified previously for each subject.

Subjects and Methods

Verapamil was formulated from a 2.5-mg/ml intravenous solution by diluting it 1:1 with phosphate buffered saline, and adjusting the pH to 7.0. The final concentration was 1.25 mg/ml. This formulation was first tested in rabbit eyes for ocular safety. No ill effects were observed.

Phase 1—Fifteen volunteers in good health (nine women and six men with a mean ± S.E.M. age of 59 ± 18 years) who were not receiving any ocular medication participated in the first phase of this study. Informed consent was obtained. Ocular hypertension had been diagnosed in all subjects, but no subject required antiglaucoma medication. No other ophthalmic disorders were diagnosed in these subjects.

Five minutes after a baseline measurement was taken by applanation tonometry, a 40-μl drop of verapamil was instilled randomly in one eye and phosphate buffered saline in the contralateral eye. After 30 minutes, a second reading was taken. Blood pressure and pulse were monitored before and after verapamil administration in order to determine if this calcium channel blocker had any cardiovascular side effects. The subjects described the level of comfort upon instillation and during the test period, and any other notable subjective effects.

Phase 2—Twelve ocular hypertensive subjects (nine women and three men with a mean ± S.E.M. age of 61 ± 17 years) volunteered for the second phase of the study, in which the duration of verapamil's effects was investigated. Informed consent was obtained. Before the administration of verapamil, natural diurnal curves were defined for each subject individually by measuring their intraocular pressure every two hours for 12 hours. On the test day, after a baseline measurement was recorded, a 40-μl drop of the 1.25-mg/ml solution of verapamil was instilled randomly in one eye and phosphate buffered saline in the contralateral eye. Pressures were then measured every two hours for ten hours.

All subject information was recorded on standard data forms and entered into a computerized database for analysis.

Results

Phase 1—The mean ± S.E.M. baseline pressure was 24.6 ± 0.900 mm Hg in the treated eye and 23.0 ± 0.900 mm Hg in the untreated eye. After 30 minutes, 14 of the 15 subjects showed a reduced pressure in the verapamil-treated eye, and 11 of the 15 subjects showed a reduced pressure in the untreated eye. Mean intraocular pressure was 20.8 ± 1.10 mm Hg in the treated eye and 21.4 ± 1.10 mm Hg in the untreated eye (Fig. 1).

By both parametric (paired two-tailed *t*-test) and nonparametric (two-tailed paired sign rank test) analysis, the mean change from baseline to 30 minutes after verapamil was statistically significant (*t*-test: treated eye, $P = .0007$ and untreated eye, $P = .005$; sign rank test: both eyes, $P < .01$).

None of the subjects showed any ocular side effects or change in blood pressure or pulse after the instillation of verapamil.

Phase 2—When the duration of verapamil's effect was investigated in 12 volunteers, a statistically significant reduction ($P < .05$) in intraocular pressure was noted at two, four, six,

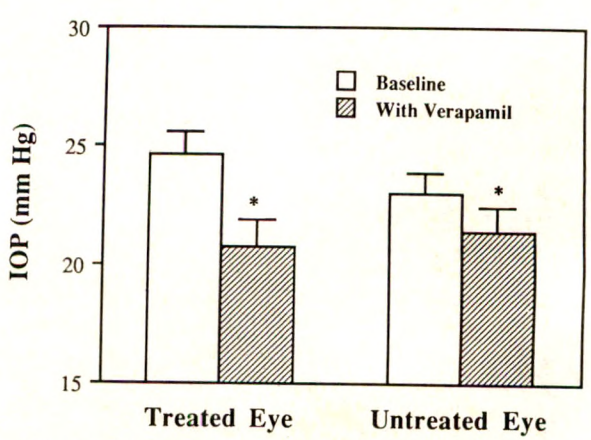


Fig. 1 (Abelson, Gilbert, and Smith). The mean ± S.E.M. intraocular pressure (IOP) measured in 15 ocular hypertensive subjects before and after unilateral topical administration of verapamil, 1.25 mg/ml. Asterisk, $P = .0007$ for the treated eye, and $P = .005$ for the untreated eye by a two-tailed paired *t*-test, or $P < .01$ for either eye by a two-tailed paired sign rank test.

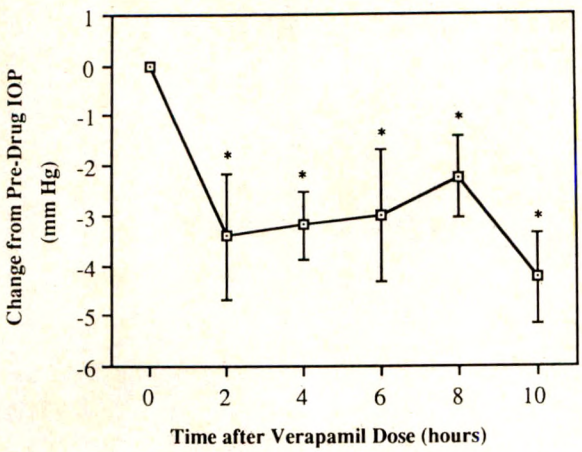


Fig. 2 (Abelson, Gilbert, and Smith). The mean ± S.E.M. change over time in intraocular pressure (IOP) from predrug baseline values to that measured after unilateral topical administration of verapamil, 1.25 mg/ml, in 12 ocular hypertensive subjects. Asterisk, Statistically significant difference from predrug control pressures ($P < .05$).

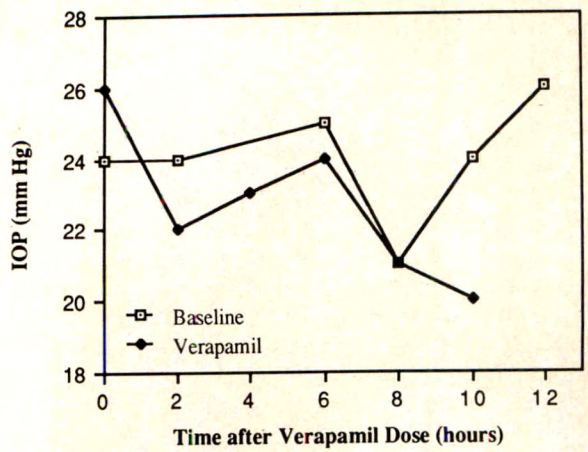


Fig. 3 (Abelson, Gilbert, and Smith). The baseline diurnal variation of intraocular pressure (IOP) measured with and without topical administration of verapamil, 1.25 mg/ml, in one eye of an untreated ocular hypertensive subject.

eight, and ten hours after administration in the treated eye (Fig. 2), and at four and six hours after administration in the untreated eye. Statistical analysis showed that the level of pressure reduction produced in the treated eye was maintained throughout the ten-hour period.

The diurnal curve of intraocular pressure for the treated eye of a selected subject with and without verapamil showed that except at the eight-hour reading, the curve was consistently lower at each time point, and each reading was also significantly reduced when compared to the baseline pressure (Fig. 3). The change from baseline untreated diurnal pressures after unilateral instillation of verapamil was significant at two, four, six, and ten hours ($P < .05$) (Fig. 4).

Discussion

Calcium channel blockers have been investigated for use in many disorders other than cardiovascular disease. We found that verapamil elicited a significant reduction in intraocular pressure in subjects with ocular hypertension. This finding is supported by a previous study in which oral administration of nitrendipine caused a significant drop in intraocular pressure.[3] The mechanism of this effect was suggested to be the concomitant peripheral vasodilation induced by systemic nitrendipine. In our study, topical verapamil caused no cardiovascular changes in subjects, suggesting that the effect observed was not the result of systemic vasodilation.

These results conflict with those of Beatty and associates,[4] who found a slight increase in pressure (1 or 2 mm Hg) in humans who had

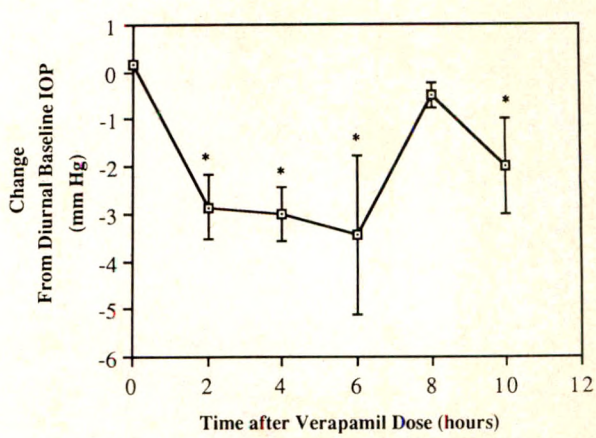


Fig. 4 (Abelson, Gilbert, and Smith). The change (mean ± S.E.M.) from baseline untreated diurnal pressures measured over a ten-hour time period after unilateral topical administration of verapamil, 1.25 mg/ml, in 12 ocular hypertensive subjects. Asterisk, Statistically significant difference from control diurnal pressures measured at the same time on a previous day ($P < .05$).

received topical verapamil. However, Beatty and associates used 1% and 2% verapamil, a ten- and 20-fold increase from the 0.125% concentration we used. Compensatory mechanisms may be responsible for this biphasic, dose-dependent response.

The most obvious explanation for verapamil's ocular hypotensive effect is local arterial and venous dilatation. Verapamil inhibits the intracellular uptake of calcium by inactivating the inner phosphorylation-dependent calcium gate of the cellular membrane.[5] By blocking the inner gate of calcium influx, contraction is inhibited and vasodilation occurs.[6] A local reduction of blood pressure is known to decrease intraocular pressure by decreasing aqueous humor inflow.[7]

Other more obscure mechanisms for verapamil's effect on intraocular pressure may, however, play a role. Gap junctions, possibly regulated by calcium, exist between nonpigmented and pigmented ciliary epithelial cells.[8] Verapamil may interfere with these gap junctions, altering cellular permeability of the ciliary epithelium, and thus inhibiting normal aqueous humor inflow.

Verapamil may also alter the cyclic adenosine monophosphate content via an effect on calcium in ciliary epithelial cells, thereby affecting intraocular pressure through a decrease in aqueous humor inflow, as with cholera toxin or forskolin, or an increase in outflow facility, as with adrenergic agents.[9]

The pharmacologic profile of different calcium channel antagonists is varied, creating the need for different classes of these agents based on their activity rather than structure.[10] While only the cardiovascular effects of these agents have been clearly defined, selective ocular hypotensive activity may also exist. This theory may be supported by the finding that diltiazem, an antagonist in a different class from verapamil or nitrendipine, did not lower intraocular pressure in a pilot study of ten ocular hypertensive subjects (unpublished data). Furthermore, while verapamil and nitrendipine are also in different classes, the spectrum of their cardiovascular effects is similar to each other.[10] The major difference between diltiazem and these agents is that diltiazem does not have a negative inotropic effect.[10] How this cardiovascular effect may relate to an ocular hypotensive effect is unknown.

As with all topical drugs, systemic absorption may occur with topical verapamil usage, and along with it, side effects associated with systemic use. Similar to timolol, which has to be used with caution in patients with diseases of cardiac depression, the use of verapamil also necessitates this precaution. Furthermore, the combination of a beta-adrenergic antagonist and a calcium channel blocker should be avoided because of their additive cardiac depressant effects.

An unexpected finding in this study was the bilateral nature of verapamil's effect when administered to only one eye. It appears that in this concentration, and with a lack of systemic cardiovascular effects, the contralateral activity was not the result of systemic action. However, the possibility of a small quantity of the agent entering the bloodstream after absorption by conjunctival and nasal mucosal blood vessels, a route that bypasses hepatic metabolism, cannot be ruled out. This has also been reported for the ocular hypotensive effect of unilaterally instilled beta-adrenergic antagonists.[11,12] This is a consistent finding that may also have significance regarding the autonomic nervous system's role in maintaining bilateral intraocular pressure.[13,14]

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Ophthalmic miniature

The door opened.

The door closed.

The silent, voluble, noisy, frightened, greedy, guilty, venal, wary, cunning, wily, stupid, apathetic, uncaring, insane, trembling in agony, going deaf, going blind, just born and doomed, screaming for no pain, wincing, cowardly, stoic, shabby, shameless, overpowered with modesty, hating, tangled, hysterical, smiling, dishonest, thieving, lying, helpless, filthy, shambling, racing, young, old, middle-aged, always the eyes, the eyes frightened and waiting, dissimulating, begging, secret and naked, the stream, the shuffling stream passed into the office, showed their tissues, exhibited their sores, voice after voice, face after face, body after body, cavity and cavity, lump and hollow, body and soul.

And then the day ended.

It was dark.

The first day was over.

Morton Thompson, *Not As A Stranger*
New York, Charles Scribner's Sons, 1954, p. 393

Nuclear Sclerosis After Vitrectomy for Idiopathic Epiretinal Membranes

Serge de Bustros, M.D., John T. Thompson, M.D., Ronald G. Michels, M.D., Cheryl Enger, M.S., Thomas A. Rice, M.D., and Bert M. Glaser, M.D.

We performed a retrospective analysis of lens changes occurring after vitrectomy for idiopathic epiretinal membranes causing macular pucker on 75 consecutive phakic eyes. Thirty-five eyes (47%) had appearance or progression of nuclear sclerosis. There were no changes in anterior subcapsular cataracts and three eyes (4%) had minimal changes in posterior subcapsular cataracts.

Based on univariate analysis, presence of preoperative nuclear sclerosis, length of follow-up period, and surgeon were found to be associated with the occurrence or progression of nuclear sclerosis. Differences between surgeons were largely accounted for by the difference in proportions with preoperative nuclear sclerosis, and differing lengths of follow-up. Kaplan-Meier life table analysis performed on 53 eyes with examination of fellow eyes and longer follow-up showed significantly more nuclear sclerosis in the operated on eye when compared to the fellow eye (log-rank test, $P < .0001$).

NUCLEAR SCLEROTIC lens changes have been shown to develop or progress after vitrectomy for epiretinal membranes affecting the macula (macular pucker).[1-4] Many of these eyes had previous or concurrent problems, such as uveitis, trauma, or a history of retinal detachment. Therefore, the association between vitrectomy and later cataract changes is uncertain. To clarify this association, we analyzed the lens changes occurring after vitrectomy performed for idiopathic epiretinal membranes causing macular pucker. These eyes had no associated ocular disorders other than posterior vitreous detachment in some cases.

Accepted for publication Dec. 3, 1987.

From the Wilmer Ophthalmological Institute, Johns Hopkins University, Baltimore (Drs. de Bustros, Michels, and Glaser and Ms. Enger); the Department of Ophthalmology, Yale University, New Haven (Dr. Thompson); and the Department of Ophthalmology, Case Western Reserve University, School of Medicine, Cleveland (Dr. Rice). This study was presented in part at the Association for Research in Vision and Ophthalmology meeting, May 8, 1987, Sarasota, Florida.

Reprint requests to Serge de Bustros, M.D., Maumenee 115, 600 N. Wolfe St., Baltimore, MD 21205.

Material and Methods

We reviewed retrospectively the records of 75 consecutive cases of idiopathic epiretinal membranes in phakic eyes affecting the macula that had been treated by vitrectomy and removal of the epiretinal tissue. These patients had no history of previous ocular surgery, and no known ocular disorder other than macular pucker and posterior vitreous detachment in some eyes. There were 34 males and 41 females. The patients ranged in age from 16 to 81 years (mean, 63 years; median, 66 years) at the time of surgery. The right eye was involved in 41 patients and the left eye in 34 patients. Preoperative visual acuity ranged from 20/50 to hand motions at 5 feet. The follow-up interval ranged from six months to 65 months (mean, 15 months; median, 11 months).

The vitrectomy techniques used to treat these patients have been previously reported.[1-5] The posterior one half to two thirds of the vitreous gel was removed, and the epiretinal membrane was then removed with a vitreoretinal pick and forceps. The intraocular portion of the operation took approximately 15 minutes, and the volume of irrigating solution used was usually 25 to 75 ml.

Two of us (R.G.M. and T.A.R.) performed all of the operations. One of us (T.A.R.) used the commercially available BSS Plus infusion solution (Alcon); the other (R.G.M.) used a special infusion solution prepared by the hospital

pharmacy. This infusion solution was similar to the glutathione-bicarbonate-Ringer's solution developed by Edelhauser and coworkers,[6-8] except that it contained 500 mg/dl of glucose.

For each case, factors related to the preoperative examination, operative procedure, and postoperative examination were tabulated. Items recorded from the history and preoperative examination included age, sex, eye, visual acuity, type and severity of lens opacity, intraocular pressure, and posterior vitreous separation. Items recorded from the operative procedure included the surgeon, type of infusion solution used, intraoperative complications, and use of intraocular air. Items recorded from the postoperative record included postoperative complications, any additional surgery, type and severity of any lens opacity, best postoperative visual acuity, final postoperative visual acuity, details of the fundus examination, and primary cause of any decrease in visual acuity occurring postoperatively.

The lens changes were characterized as to location and severity based on biomicroscopy. The locations were designated as cortical or anterior subcapsular cataract, nuclear sclerosis, and posterior subcapsular cataract. The severity of lens opacities was graded as none, mild, moderate, or severe.

Preoperative and intraoperative factors were examined for possible associations with the development or progression of postoperative cataract changes. Eyes were divided into two groups: those with no lens opacities or minimal changes; and those with mild, moderate, or severe changes. Categorical factors were analyzed using the chi-square test. The Mantel-Haenszel test was used to test for the consistency of associations across subgroups (surgeons). Group means were compared with Student's *t*-test.

To verify that no bias was introduced by the varying lengths of follow-up, the prognostic factors were examined for balance between those eyes followed up for longer than 11 months (median) and those followed for a shorter period of time. There was no difference between these groups with regard to preexisting nuclear sclerosis, age, sex, or use of intraocular air.

Detailed information was also available on the fellow eye in 53 patients. A Kaplan-Meier life table was constructed showing the rate of lens changes in the operated on eye, and this was compared to changes in the fellow eyes using the log-rank test.

TABLE
FACTORS ASSOCIATED WITH NUCLEAR SCLEROTIC LENS CHANGES (UNIVARIATE ANALYSIS)

PREOPERATIVE FACTOR	NO NUCLEAR SCLEROTIC LENS CHANGES (N = 40) NO.	(%)	NUCLEAR SCLEROTIC LENS CHANGES (N = 35) NO.	(%)	P VALUE
No preoperative nuclear sclerosis	18	(38)	29	(62)	
Preoperative nuclear sclerosis	22	(79)	6	(21)	.0007
Surgeon					
R.G.M.	18	(37)	31	(63)	
T.A.R.	22	(85)	4	(15)	.0001
No air/gas used	34	(52)	31	(48)	
Air/gas used	6	(60)	4	(40)	.65

Results

Postoperatively, 35 (47%) of the 75 eyes had appearance or progression of nuclear sclerosis. The amount of nuclear sclerosis was mild in 17 eyes (23%), moderate in 14 eyes (19%), and severe in four eyes (5%). In contrast, there were no anterior subcapsular cataract changes, and only three eyes (4%) developed posterior subcapsular cataract changes.

Absent preoperative nuclear sclerosis was found to be significantly associated with the occurrence or progression of postoperative nuclear sclerosis ($P = .0007$) (Table). There was no difference in age of the patients at time of surgery comparing eyes with and without progressive nuclear sclerosis (64.2 ± 7.2 years vs 62.8 ± 13.7 years, respectively). Intraoperative use of air or sulfur hexafluoride gas showed no association with later lens changes. The follow-up time was significantly longer in the group that showed occurrence or progression of postoperative nuclear sclerosis (19.5 ± 14.9 months) than in the group that showed no lens changes (10.4 ± 5.2 months) ($P < .001$). There was also a significant difference between surgeons in the proportion of eyes with postoperative cataract changes. However, the surgeon who had patients with the higher incidence of nuclear sclerosis progression (R.G.M.) also had patients with a significantly longer follow-up period than the other surgeon (17 vs 11 months) ($P = .017$). Additionally, the surgeon

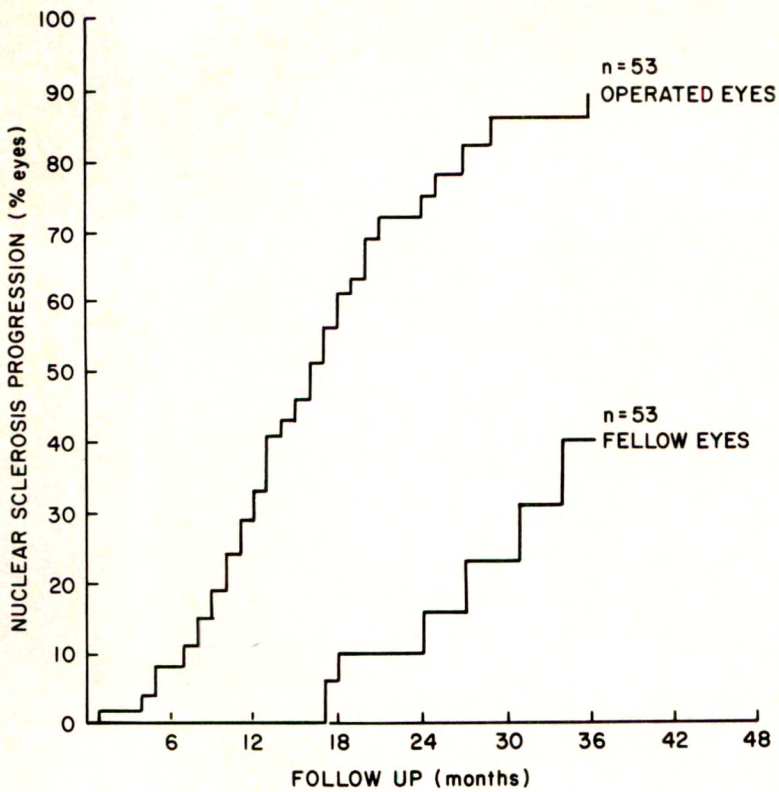


Figure (de Bustros and associates). Kaplan-Meier life table analysis showing significant difference in the rate of de novo development or progression of nuclear sclerosis in operated on eyes compared to fellow eyes (log-rank test, $P < .0001$). Of the 53 operated on eyes, there were 30, ten, and five still at risk at 12, 24, and 36 months, respectively. Among the fellow eyes, there were 39, 17, and seven eyes still at risk at 12, 24, and 36 months, respectively.

with patients who had a lower incidence of nuclear sclerosis progression (T.A.R.) had a significantly higher proportion of patients with nuclear sclerosis preoperatively than the other surgeon (69% vs 20%, $P = .0003$). These two factors explain, at least partially, the difference between the results achieved by the two surgeons.

Because of the seemingly large difference in results between surgeons, the data were stratified by surgeon, resulting in a borderline significant association between preoperative nuclear sclerosis and the progression of nuclear sclerosis (Mantel-Haenszel, $P = .056$). However, within each subgroup by surgeon, length of follow-up remained significantly longer in the group that showed lens changes ($P < .02$).

Of the 53 patients in whom detailed examination of the fellow eyes had been performed and long follow-up was available, 38 of the operated on eyes (72%) had appearance or progression of nuclear sclerosis, compared to nine (17%) of the fellow eyes ($P < .001$). Kaplan-Meier life table analysis showed a highly significant difference in the rate of de novo development or progression of nuclear sclerosis comparing the surgical eye to the fellow eye (log-rank test, $P < .0001$) (Figure). By 12 months postoperatively, with 30 out of the 53 eyes still at risk, the cumulative incidence of nuclear sclerotic changes was 31% (95% confidence interval: 20% to 46%), compared to 0% in the 39 at-risk fellow eyes. By 24 months postoperatively, for the ten operated on eyes at risk the cumulative incidence was 72% (95% confidence interval: 58% to 85%), compared to 15% in the 17 fellow eyes (95% confidence interval: 6% to 36%). Similar life table analyses and log-rank tests comparing surgical and fellow eyes were performed for each surgeon separately, and showed similar results. The log-rank test comparing the cumulative event rates found no significant difference between surgeons ($P = .35$).

The influence of nuclear sclerosis on postoperative vision was determined by measuring visual acuity at different time intervals, by examining the macula for recurrence of epiretinal membranes or other abnormalities, and by using the potential visual acuity meter. Using these methods, nuclear sclerosis was thought to be the primary reason causing some further deterioration of the final visual acuity in 25 eyes (33%). Other factors limiting final visual acuity

included residual traction retinal detachment involving the macula (one eye), cystoid macular edema (ten eyes), other macular edema (eight eyes), residual or recurrent epiretinal membrane with distortion of the macula (two eyes), and drusen or other retinal pigment epithelial changes (two eyes).

Discussion

Idiopathic epiretinal membranes causing macular pucker and impaired vision are a well-known acquired clinical condition. These eyes usually have no associated ocular disorder other than a posterior vitreous detachment in some eyes. Vitreous surgery is now used to remove the epiretinal membrane in selected cases if there is substantial visual loss.

Most complications of vitrectomy for macular pucker, including endophthalmitis, vitreous hemorrhage, and retinal tear or detachment, are rare. However, later lens opacities are more common, and this is almost always nuclear sclerosis. Nuclear sclerosis is caused by the gradual accumulation of insoluble lens proteins and pigments, which result in loss of transparency and color changes in the lens nucleus ranging from yellow to brown. Nuclear sclerosis is a common, age-related change occurring in the lens, and there is often nearly symmetric involvement of both eyes. Life table analysis of both eyes in 53 patients in this series showed progression of nuclear sclerosis mainly in the operated on eye, indicating that this is a complication of surgery rather than an unrelated change.

In contrast, vitrectomy was not associated with a high incidence of cortical or anterior subcapsular cataract changes. Appearance or progression of posterior subcapsular cataracts occurred in only 4% of our cases. The posterior capsule is in direct contact with substances in the vitreous cavity, and therefore physical or chemical damage might interfere with proper metabolism of the subjacent lens fibers. Possible causes for the posterior subcapsular changes include mechanical lens damage during surgery, use of intravitreal gas, or metabolic damage caused by the irrigating solution.

The occurrence or progression of nuclear sclerosis after vitrectomy for epiretinal membranes has been described by various authors.[1-4] Margherio and associates[2] reported a low incidence (12.5%) and attributed it to multiple factors, including shorter operating time, distance of the infusion port from the lens, type of irrigating fluid used, and a surgical technique that spared the anterior vitreous behind the lens. Michels[1] reported a 34% incidence in 90 cases, some of which are included in the present, expanded study. McDonald, Verre, and Aaberg,[3] using similar surgical techniques, observed postoperative nuclear sclerosis in 13 of 33 cases of idiopathic macular pucker. Poliner and colleagues[4] reported a 50% incidence of postoperative cataract changes in 40 eyes, with an average follow-up of 18 months.

Nuclear sclerosis is a progressive phenomenon that worsens with time. This complication occurred in an increasingly higher percentage of our cases as the length of follow-up increased. Absence of preoperative nuclear sclerosis also had an association with postoperative nuclear sclerotic changes that was of borderline statistical significance, probably because these eyes have more potential for change. It is our clinical impression that younger patients have a lower incidence of postoperative nuclear sclerosis. However, this could not be demonstrated in our current study, probably because of the small number of young patients. The reason for the occurrence of postoperative nuclear sclerosis is unclear, and cannot be satisfactorily explained by differences in the published surgical techniques.

High glucose has been shown to cause nonenzymatic browning of lens proteins and cataract formation both in vitro and in vivo using rat and bovine lenses after exposure for several days.[9,10] It is unlikely that intraoperative exposure to high glucose infusion of about 30 minutes caused lens browning and nuclear sclerosis in our patients. We found no significant difference in the incidence of nuclear sclerosis between two surgeons in this study using different infusion solutions when corrected for the length of follow-up. Unfiltered light from the operating microscope or light from the fiberoptic probe reflected from the fundus are possible factors in the pathogenesis of nuclear sclerosis that deserve further investigation (Steve Charles, M.D., oral communication, July 13, 1987).

We recognize the limitations of this analysis. Ideally, a prospective study with more objective assessment of lens changes and possible randomization of certain factors would have been preferable. Nevertheless, this is, to the best of our knowledge, the only study address-

ing the issue of nuclear sclerosis after vitrectomy in a group of eyes with no previous ocular disease or surgery other than an idiopathic epiretinal membrane. Our findings suggesting a worsening of nuclear sclerosis after vitrectomy have important implications, especially in situations where vitrectomy is selected as an option, such as in the treatment of primary rhegmatogenous retinal detachment.

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OPHTHALMIC MINIATURE

"In addition to these streaks, does your vision show anything else you're not accustomed to?"

"In a way, I guess," Cahill answered. "If you can follow me, I'll try to tell you about it. Supposin' you had yourself a sheet of black paper, and on top of it you was to put a crossword puzzle. And suppose you was to take out, every now and then, one of them little squares, so that there was only black where the square was. Wouldn't be no letter there, no place for a letter. Nothin' but a black square. This keeps goin' on. An then pieces of fire keep shootin' through the puzzle all the time."

"Some puzzle. Each one of those pieces is a part of your eyesight dying. Why the pieces are square in your case, I'm damned if I know."

James Dickey, *Alnilam*
Garden City, New York, Doubleday & Company, Inc., 1987, p. 15

Twin Vessels in von Hippel-Lindau Disease

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Mies J. van de Vooren, M.D., Danielle F. Majoor-Krakauer, M.D.,
and Anton R. Wiegel, M.D.

We examined ten patients from three families with von Hippel-Lindau disease and 26 of their at-risk relatives for the presence of twin vessels, defined as a paired retinal arteriole and venule that are separated by less than the diameter of one venule and extend for a distance of more than one disk diameter. They were compared with 36 age- and sex-matched controls. Of the 36 subjects in the study group, 23 had twin vessels compared with two controls ($P < 10^{-6}$). Of the ten patients, nine (14 eyes) had twin vessels; no twin vessels were found in their controls ($P = 5.9 \times 10^{-5}$). Fourteen at-risk relatives and two of their controls had twin vessels ($P = 9.4 \times 10^{-4}$).

THERE ARE THREE patterns of vascularization in the normal human eye: the juxtaposed arterioles and venules of the conjunctiva, the staggered arterioles and venules of the retina, and the sinusoidal venules and arterioles of the choroid.[1] The adult retinal vascular pattern is established several months after birth and matures during the next several years.[2] The larger arterioles and venules of the retina share a common territory but normally have no close juxtaposition one to another, as do conjunctival or connective tissue vessels.[1,3]

In retinal angiomatosis, or von Hippel's disease, there are single or multiple hamartomatous capillary masses in the retina, each supplied and drained respectively by a widely dilated arteriole and venule. In the autosomal dominant hereditary hemangioblastomatosis, or von Hippel-Lindau disease, retinal angiomas, hemangioblastoma of the central nervous system, and cysts and benign or malignant tumors in several visceral organs may be present.[4,5] The diagnosis of von Hippel-Lindau disease is made when either a retinal angioma or a central nervous system hemangioblastoma occurs together with one or more visceral cysts or tumors in one patient or when a single lesion of the von Hippel-Lindau complex is found in a relative at risk.[4] Eventually, 44% to 64% of the patients with von Hippel-Lindau disease develop one or more retinal angiomas, 52% to 69% develop central nervous system hemangioblastoma, 25% develop renal cell carcinoma, approximately 33% develop renal or pancreatic cysts, 17% develop polycythemia, and 7% develop pheochromocytoma.[6-8] In the early stages, most of these lesions are asymptomatic.[8] Regular screening for lesions of von Hippel-Lindau disease in patients and relatives at risk provides earlier detection and permits better treatment. Regular ophthalmoscopic, neurologic, and internal examinations are therefore indicated, including central nervous system and abdominal computed tomographic scans, abdominal echography, and tests for pheochromocytoma.[7]

Examining members of a family with von Hippel-Lindau disease, one of us noted a strikingly close pairing of retinal arterioles and venules, which we called twin vessels. Twin vessels occurred in patients and at-risk family members. This led us to investigate the significance of this phenomenon to learn if there was an association between the presence of twin vessels and the occurrence of von Hippel-Lindau disease.

Subjects and Methods

Twin vessels were defined as a pair of vessels, one retinal arteriole and one venule, separated by less than one venule width, that run a parallel course for more than 1 disk diameter; sometimes the vessels may cross each other.

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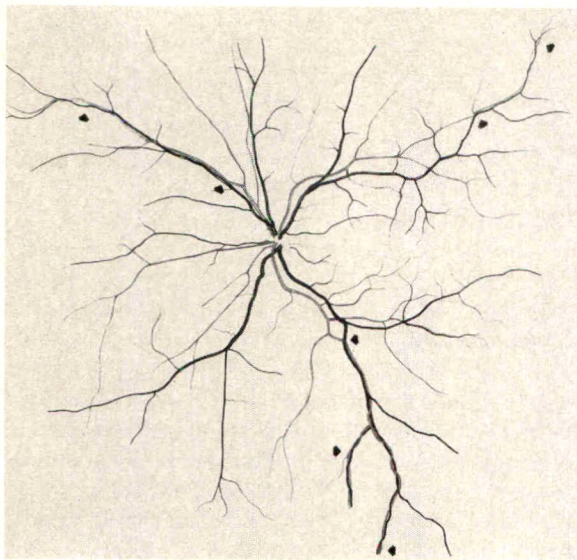


Fig. 1 (de Jong and associates). Sketch of vessels in left eye of Case IV-5, pedigree 1. Arrows indicate twin vessels.

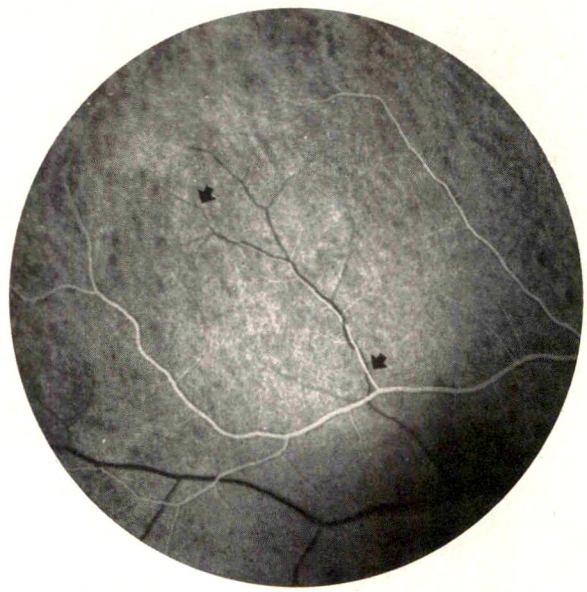


Fig. 2 (de Jong and associates). Twin vessels (between arrows) in Case III-4, pedigree 1.

Because crowding of vessels near the optic disk might simulate twin vessels, twin vessels were only scored as such when located at least 2 disk diameters distant from the disk (Figs. 1 through 4).

In three unrelated families with von Hippel-Lindau disease, all patients and at-risk relatives willing to cooperate were examined for the presence of retinal angiomas and twin vessels. They underwent a complete ophthalmic examination, including indirect ophthalmoscopy after pupillary dilation. In selected cases a three-mirror Goldmann contact lens was used. When possible, color photographs were taken. Fluorescein angiography was performed in four eyes.

A family history was recorded and all patients and at-risk family members underwent a multidisciplinary screening, according to a previously described protocol.[6] The screening included neurologic examination and computed tomographic scan of the brain of all patients

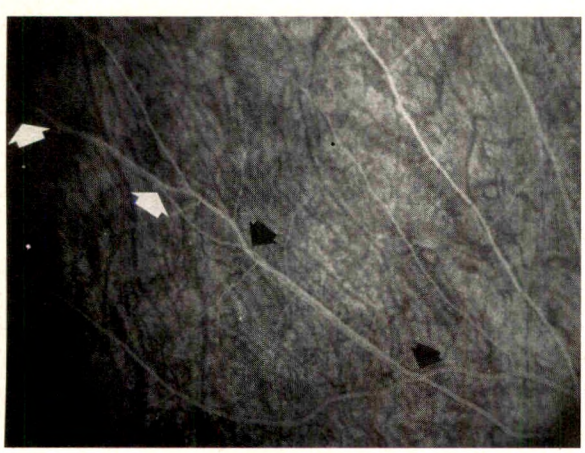


Fig. 3 (de Jong and associates). Fluorescein angiogram of twin vessel in at-risk member III-9, pedigree 2. Note that the twin vessel between the black arrows splits and comes together again at the white arrows.

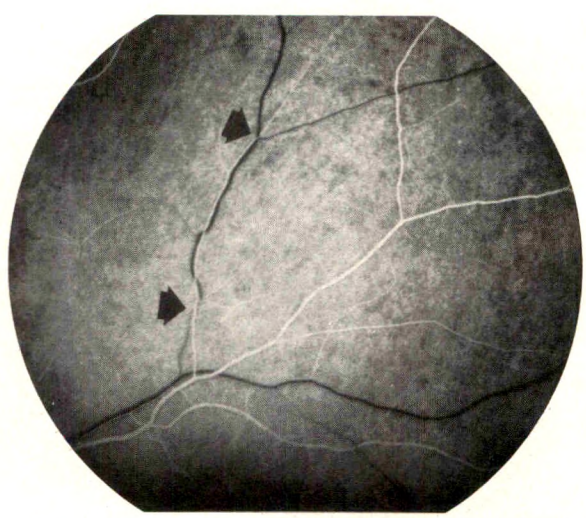


Fig. 4 (de Jong and associates). Angiogram of twin vessel (between arrows) in left eye of control patient of same age and sex as at-risk member II-3, pedigree 1.

and at-risk relatives over 10 years old. Computed tomography of the spinal cord or medulla was indicated only if neurologic abnormalities were found and the computed tomographic scan of the head was normal. Patients and at-risk relatives were also examined for systemic lesions by abdominal echography or computed tomography as well as tests for pheochromocytoma. Data from patients who had died were obtained from their files. From these combined examinations, it was possible to designate patients and at-risk members, according to the previously mentioned definition.

Age- and sex-matched controls with clear media and without retinal vascular disorders were recruited from our ophthalmologic clinic. The first eligible subject examined at the clinic after examination of a member of a von Hippel-Lindau family was used as a control. All subjects gave informed consent for pupillary dilation and indirect ophthalmoscopy, and all were examined by one of us (P.T.V.M.J.). The examiner was not masked to the identity of the subject. For statistical analysis we used Fisher's exact one-tailed test and the chi-square test with Yates' correction factor.

Results

Twin vessels looked like normal retinal vessels except for their adjacent course. The number of twin vessels ranged from one to six per affected eye (average, two). Twin vessels could be present in all regions of the fundus, including the far periphery. There were never afferent or efferent vessels connected with a visible angioma. The maximum extent of twin vessels was 8 disk diameters. In general, the diameter of the arteriole and venule forming the twin vessel corresponded to the diameter of the vessels in the same retinal area. The diameter between different pairs of twin vessels and sometimes within one twin vessel pair could vary. In this case (Fig. 3), the arteriole was the smaller vessel. On fluorescein angiography the twin vessels showed normal circulation times in comparison with vessels of corresponding diameter in the same region. There was no vascular staining in the late phase and no hemorrhages or exudates in their vicinity. In some eyes the retinal vessels, also nontwin vessels, were radially stretched from the disk towards the periphery without the usual twisted course.

Ophthalmic examination was performed on 36 subjects from three von Hippel-Lindau families and 36 age- and sex-matched controls. Twin vessels were found in 23 subjects (34 eyes) from the affected families and in two controls (two eyes) ($P < 10^{-6}$) (Table).

Thorough ophthalmic, neurologic, and systemic screening of the 36 cooperating members of these three von Hippel-Lindau families yielded ten patients and 26 at-risk relatives (Fig. 5). Nine of the ten patients had retinal angiomas in 13 eyes and nine of the ten pa-

TABLE
RESULTS OF OPHTHALMOSCOPY

FINDING	VON HIPPEL-LINDAU DISEASE		AT-RISK RELATIVES		CONTROLS	
	NO. OF PATIENTS (N = 10)	NO. OF EYES (N = 19)	NO. OF SUBJECTS (N = 26)	NO. OF EYES (N = 52)	NO. OF SUBJECTS (N = 36)	NO. OF EYES (N = 72)
Twin vessels	9*	14†	14‡	20§	2	2
Retinal angiomas	9	13	0	0	0	0
Retinal angioma and twin vessel in same eye‖	7	10	0	0	0	0
Retinal angioma, no twin vessel in same eye‖	3	3	0	0	0	0

*$P = 5.9 \times 10^{-5}$ as compared with controls.
†$P = 7.6 \times 10^{-6}$ as compared with controls.
‡$P = 9.4 \times 10^{-4}$ as compared with controls.
§$P = 4.5 \times 10^{-5}$ as compared with controls.
‖Numbers do not add. Case II-2, pedigree 1, belongs to both groups.

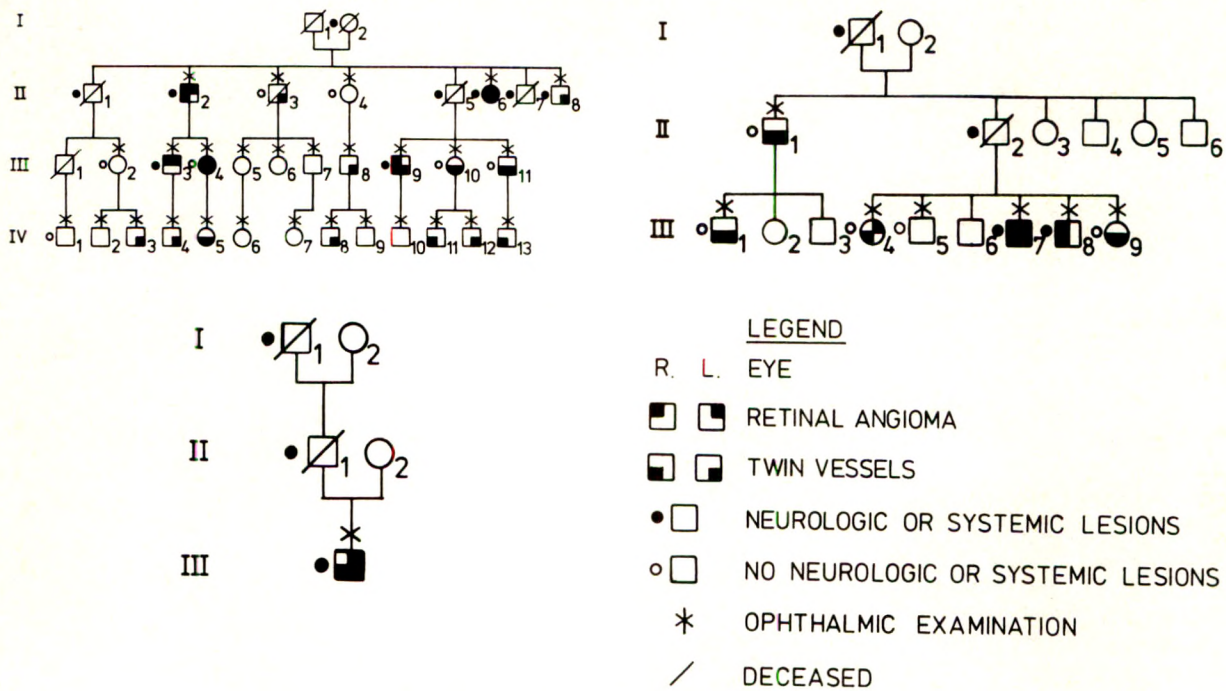


Fig. 5 (de Jong and associates). Pedigrees of three von Hippel-Lindau families. Top left, pedigree 1. Top right, pedigree 2. Bottom left, pedigree 3. All deceased members except I-1, II-3, and III-1 of pedigree 1 died of von Hippel-Lindau disease. All family members who underwent both ophthalmic, neurologic, and systemic examinations had a computed tomographic scan of the head and echography or computed tomography of the abdomen. Subjects not examined either refused or were too young. Neurologic and systemic findings from patients who died before this study were obtained from their files.

tients had twin vessels in 14 eyes (Table), although twin vessels were not always present in the same eye as the retinal angiomas. Eight of the ten patients had neurologic or systemic lesions, or both, and seven of these eight also had twin vessels.

The only patient without retinal angiomas (Case II-8, pedigree 1) had twin vessels in his left eye and a cerebellar hemangioblastoma. The only patient without twin vessels (Case III-3, pedigree 1) had retinal angiomas and a central nervous system hemangioblastoma.

Three of the nine patients with retinal angiomas (Fig. 5, pedigree 1, II-2 and III-3; pedigree 2, III-4) had one eye with retinal angiomas but no twin vessels.

In Case III-3, pedigree 1, the left eye had been enucleated at age 7 years for neovascular glaucoma secondary to complications of an angioma. This eye is represented in Figure 5 as having no twin vessels, although we cannot tell if this is correct. This was also our youngest patient with retinal angiomas.

The mean age of the patients with retinal angiomas and twin vessels was 32.4 years, whereas the mean age of the at-risk relatives with only twin vessels was 22.5 years.

In the matched controls of the ten patients, no twin vessels were found ($P = 5.9 \times 10^{-5}$).

Fourteen of the 26 at-risk relatives had twin vessels compared to two of their matched controls ($P = 9.4 \times 10^{-4}$). The youngest at-risk member with a twin vessel was 3 years old.

Discussion

The occurrence of twin vessels in 23 persons of three unrelated families with von Hippel-Lindau disease makes a coincidental vascular anomaly improbable. Twin vessels were observed in nine of the ten patients with von Hippel-Lindau disease. Approximately one half of the examined at-risk relatives had less than 50% chance of having inherited von Hippel-Lindau disease. In the at-risk relatives, however, twin vessels were detected in 14 of

the 26 subjects (54%). Only two of the 36 controls (6%) had twin vessels. These results indicate a significant association between von Hippel-Lindau disease and twin vessels, especially when one considers that the prevalence of von Hippel-Lindau disease is estimated to be 1:230,000.[9]

However, as seen in three eyes, retinal angiomas may occur without twin vessels. Therefore, even in the absence of twin vessels routine ophthalmoscopy of patients and at-risk relatives is warranted.

Twin vessels may be an ocular manifestation of von Hippel-Lindau disease. There could be a common pathogenetic pathway of retinal angiomas and twin vessels, since both originate from mesenchymal cells. Alternatively, a separate gene responsible for the development of twin vessels might be located close to the von Hippel-Lindau mutation, resulting in linkage of both traits in several families. As shown in pedigree 1 (Fig. 5), twin vessels were present in offspring of the monocular patient (III-3) and in offspring of two at-risk relatives (II-4 and III-2); however, these three subjects did not have twin vessels themselves. This could be explained either by the great variability of von Hippel-Lindau disease or by assuming that twin vessels are a separate, dominantly inherited trait with incomplete penetrance. In two other families not described here, isolated central nervous system hemangioblastoma occurred in combination with twin vessels, at present without retinal angiomas or other manifestations of von Hippel-Lindau disease. Further follow-up examinations of these patients will show whether they will develop signs of von Hippel-Lindau disease.

We believe twin vessels are a variant of the normal retinal vascular pattern. They are not pathologic vessels as they have the same diameter as the surrounding retinal arterioles and venules, do not stain or leak on fluorescein angiography, and have no pathologic exudates around them. Twin vessels were observed in patients and at-risk relatives of all ages in this study.

Retinal angiomas are the most common early manifestation of von Hippel-Lindau disease, with an average age at diagnosis of 22 years.[8] They have been described in a pathologic report of a fetal eye, and growth of a new angioma has been recorded in the seventh decade of life.[10] The youngest patient with a retinal angioma in this study was 7 years old. New angiomas were also found at a relatively advanced age in Patient II-2, pedigree 1 (age 56 years) and Patient II-6, pedigree 1 (age 50 years).

Since the retinal vascular pattern remains stable from the age of 6 months,[2] we expect that twin vessels remain stable also. Twin vessels are easily detected by ophthalmologic examination and occur in most patients with von Hippel-Lindau disease. A prospective follow-up study of a greater number of patients with von Hippel-Lindau disease and their at-risk relatives is needed to establish a definite association between twin vessels and the occcurrence of von Hippel-Lindau disease in an at-risk relative. If such an association can be demonstrated within an individual at-risk family member, the presence of twin vessels could be valuable as an early diagnostic sign of von Hippel-Lindau disease.

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Pathogenesis and Therapy of Traction Detachment in Various Retinal Vascular Diseases

Robert Machemer, M.D., and John M. Williams, Sr., M.D.

We examined six patients with retinal vasculopathies (two cases each of angiomatosis retinae [von Hippel-Lindau disease], exudative vitreoretinopathy, and Coats' disease), who developed preretinal and vitreal membranes, retinal traction detachment, and exudation under the retina. The membranes consisted of a core of collagen of various diameter fibers usually covered on both sides by cells that displayed glial cell characteristics. The retina reattached spontaneously and exudates disappeared when traction was eliminated by vitreous surgery. Membrane formation did reoccur after vitrectomy if the vessels continued to leak, leading again to traction and subretinal exudation. Treatment consisted of surgical removal of vitreal and preretinal membranes and destruction of leaking vessels.

THERE ARE SEVERAL retinal vascular diseases, such as Coats' syndrome,[1] angiomatosis retinae (von Hippel-Lindau disease),[2,3] and exudative vitreoretinopathy,[4] that lead to exudative retinal detachments. When these detachments are treated with vitreous surgery, the exudation under the retina disappears. There is a tendency to reform strands with recurrence of retinal detachments and subretinal exudates. We believe the vitreous disease is caused by the vascular disease and causes the subretinal exudates. Herein we describe several patients, their course after vitreous surgery, and the histopathologic features of the membranes formed.

Material and Methods

Six patients suffering from retinal vascular disease (two cases each of angiomatosis retinae [von Hippel-Lindau disease], exudative vitreoretinopathy, and Coats' syndrome) were found to have exudative retinal detachments and preretinal and vitreal strands causing traction on the retina. Vitreous surgery techniques were performed to remove the strands. In most cases, the vascular lesions were initially not treated. Recurrence of intraocular proliferations leading to a clinical picture similar to the initial one necessitated repeat vitreous surgery in some cases and treatment of the vascular lesions.

Ten preretinal and intravitreal membranes were excised from five of the six patients. The specimens were obtained during pars plana vitrectomy. Specimens were prepared for transmission and scanning electron microscopy using previously described methods.[5] Ten membranes (Cases 1 through 5) were analyzed by transmission electron microscopy and one membrane (Case 3) was analyzed by both transmission and scanning electron microscopy.

Case Reports

Case 1

A 35-year-old woman noted a decrease in visual acuity in her left eye. Her right eye had

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been enucleated because of the suspicion of a malignant melanoma. The pathologic findings showed a "chronic uveitis, retinal detachment, degeneration, and endophthalmitis." When the woman was seen in July 1984 visual acuity in the left eye was hand motions at 5 feet. A total retinal detachment was found, with yellow exudates under the retina. A large fleshy vascular tumor with dilated feeder vessels was noted in the periphery at the 11 o'clock meridian. A thorough examination disclosed another vascular tumor in the cerebellum. The diagnosis of von Hippel-Lindau disease was made.

Because of vitreous condensations and the appearance of traction on the retina, a vitrectomy was performed. The vitreous was found to be solid and gelatinous, and it had to be cut away piece by piece from the retina. A small retinal tear was created in the inferior periphery, which was closed with a buckle. No cryotherapy was applied to the tumor.

Two months later, visual acuity improved to 20/300. The retina was attached at the posterior pole, with heavy pigmentary changes under the retina. Extensive subretinal strand formation was seen around the disk, keeping the retina shallowly detached in this area. Remaining exudate was found nasally and inferiorly. An intense flare was noted. The eye was treated with topical corticosteroids. In December 1984 an acute glaucoma attack with iris bombé necessitated an iridectomy. In March 1985 visual acuity was reduced to counting fingers at 6 feet. A posterior subcapsular cataract had developed. A lentectomy was performed. At this time it was apparent that the retina had completely redetached, and there were new vitreous membranes that left no evidence of the previous vitrectomy. Once again, a careful membrane removal was done. This time, the vascular tumor was treated with diathermy, with additional laser treatment given postoperatively. The retina began to reattach. Visual acuity improved to 20/300, and the eye was free of flare. Three months later visual acuity deteriorated to hand motions. The retina had redetached, with some strands visible in the vitreous cavity. The vascular tumor had regained its original size and there was a heavy flare in the anterior chamber and vitreous cavity.

Histopathologic findings—Examination by transmission electron microscopy of the solid, gelatinous-appearing vitreous taken during the first vitrectomy disclosed thick membranes comprised of multiple layers of collagen fibrils, approximately 1,000 nm in diameter. No cells were seen within the membrane, except for an occasional macrophage on the surface of the tissue.

Case 2

A 36-year-old woman had noted a decrease in vision in her right eye. She had a history of poor vision in the left eye since 1974. When seen in October 1979 visual acuity was R.E.: 20/70 and L.E.: 5/200. In the right eye, preretinal proliferation and membranes that were detached from the retina, extending from the nasal aspect of the disk to the temporal superior periphery, had drawn the foveal area superiorly (Fig. 1). There was a small angioma at the 12 o'clock meridian, near the equator, with enlarged vessels leading to it. Several minute vascular abnormalities were seen in the remaining periphery. In the left eye, the disk was obscured by a dense proliferation that extended temporally and superiorly, elevating the macula in a traction detachment. Subretinal strands and exudate were seen. A cerebellar vascular tumor was found, and the diagnosis of von Hippel-Lindau disease was made. A vitrectomy was performed in the right eye to release the traction and remove membranes where possible. The vessels were not treated. Vision initially improved, but then decreased. One year later, visual acuity was R.E.: 20/100. The fovea was drawn superiorly and showed a questionable hole. Membranes again originated from the optic nerve head, extending to the superior arcade (Fig. 2). Membranes in the periphery caused localized detachments. Enlarged feeder vessels passed superiorly and disappeared underneath white preretinal tissue. Neovascularization was seen in the extreme temporal periphery.

In March 1982 visual acuity in the right eye had further decreased to 20/400. The anterior chamber and the vitreous cavity now showed a flare. Membranes extended from the disk to the temporal superior periphery, where the retina was elevated (Fig. 3). Multiple sheets of membranes extended from the retina into the vitreous cavity. Superiorly, a large feeder vessel led to a small vascular tumor, and inferonasally, another vascularized retinal lesion was found. A second vitrectomy with lentectomy was performed. It was not possible to lyse all membranes from the retina. A buckle was placed around the eye, and the vascularized lesions were carefully treated with cryoapplications. Postoperatively, visual acuity rapidly improved to 20/160 and the retina reattached (Fig. 4). In

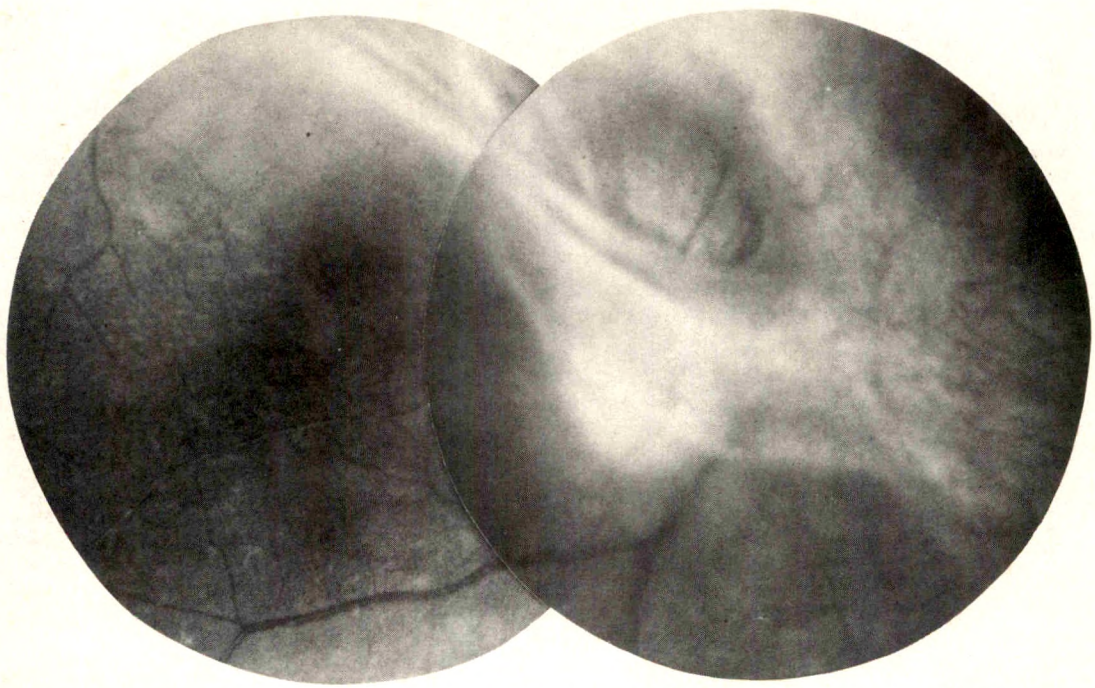


Fig. 1 (Machemer and Williams). Case 2, right eye. Fundus photograph of the posterior pole. Note preretinal proliferation and superior dragging of the fovea.

March 1985 visual acuity had decreased to light perception. Prominent proliferations extending from the disk into the peripheral vitreous cavity were seen. The retina was shallowly detached and a yellow subretinal exudate was present (Fig. 5). Several vascular tumors were found in locations that had been free of disease. Once again, a release of traction was

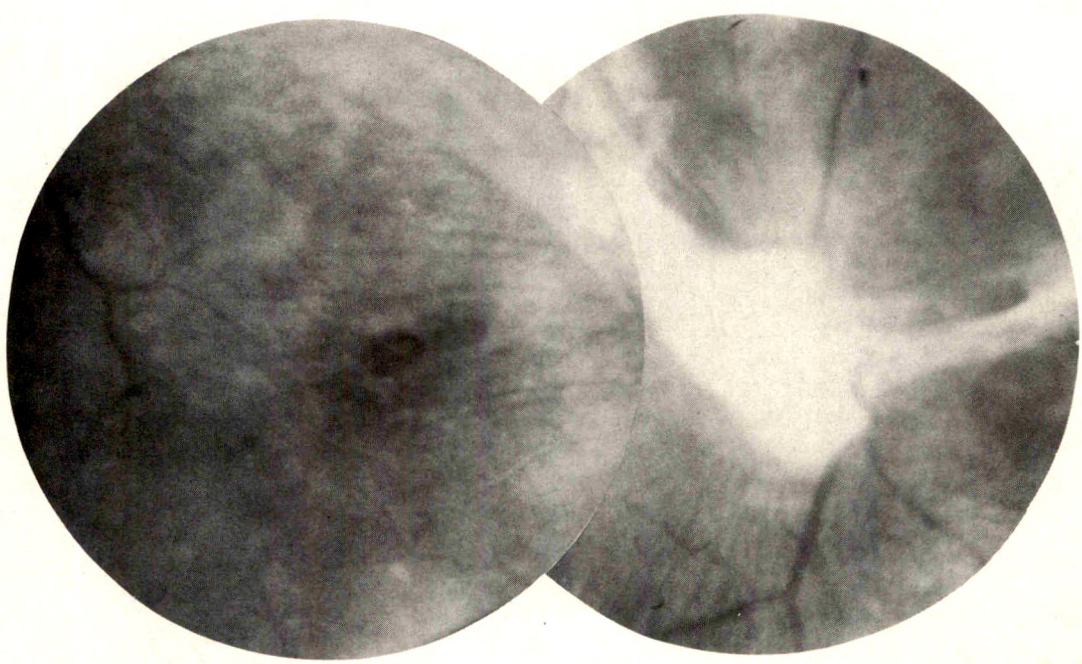


Fig. 2 (Machemer and Williams). Case 2, right eye after first vitrectomy. Note macular hole. Residual preretinal tissue is present over the disk as well as superior and nasal to it.

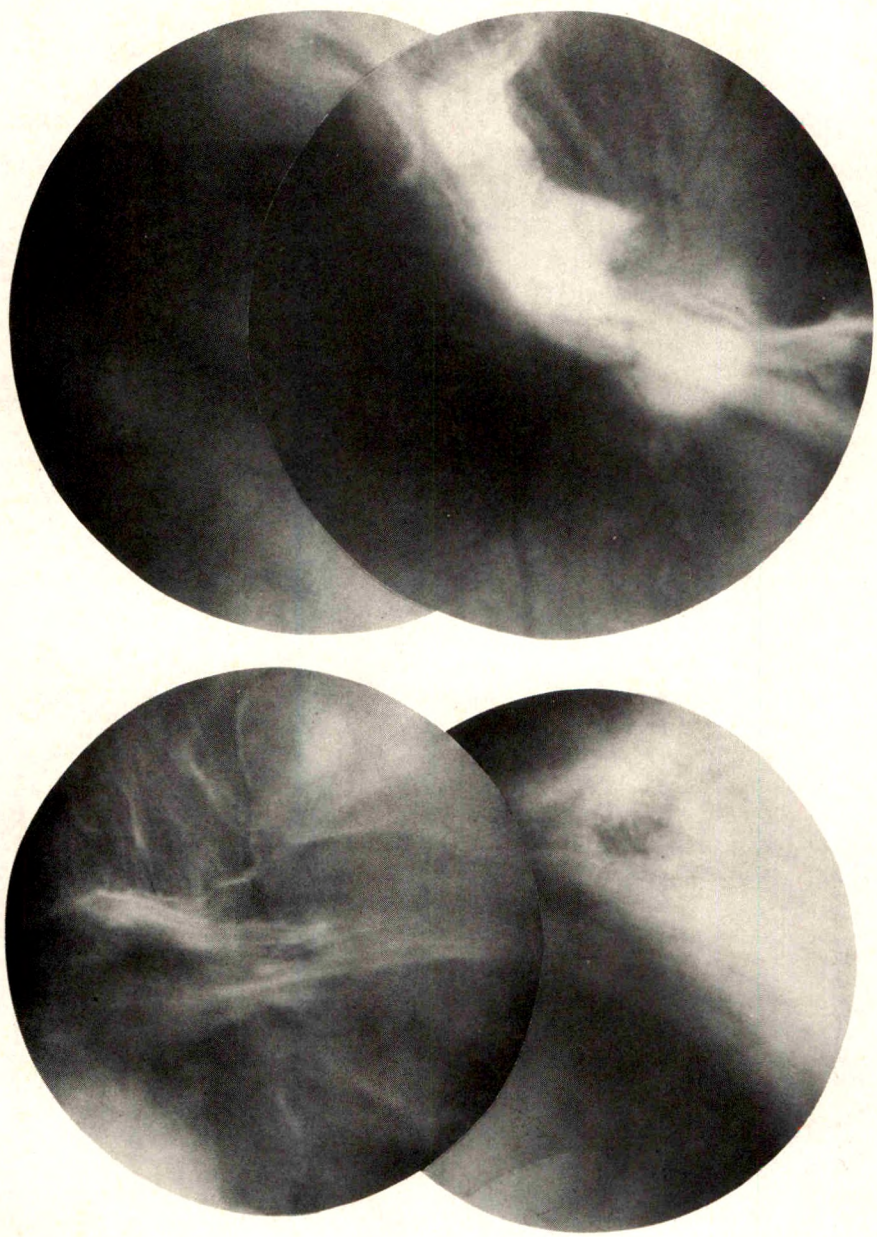


Fig. 3 (Machemer and Williams). Case 2, right eye. Top, Immediately before second vitrectomy. Note upward traction on macula and increased preretinal membrane formation. Bottom, Note extensive preretinal and intravitreal membrane formation in the periphery.

attempted with repeat vitreous surgery, all membranes were removed, and the new vascular lesions were treated with diathermy and cryoapplications. The retina did settle, but visual acuity improved only to hand motions.

Histopathologic findings—The specimens taken from the eye during the first vitrectomy showed a thick membrane with spindle-shaped cells lining either one or both surfaces (Fig. 6). The membranes peeled from the retinal surface had cells on one surface. The cytoplasm of these cells extended far beyond the nucleus and interdigitated with that of adjacent cells. Microvilli were present on the vitreal side of the cell. Cytoplasmic microfilaments 800 to 1,000 nm in diameter were seen (Fig. 7, top left), as were dilated rough endoplasmic reticulum. Hemidesmosomal attachments were present at the basal lamina-collagen matrix interface and desmosomes (Fig. 7, top right) as well as tight junctions between adjacent surface cells (Fig. 7, bottom left). Fusiform subplasma-

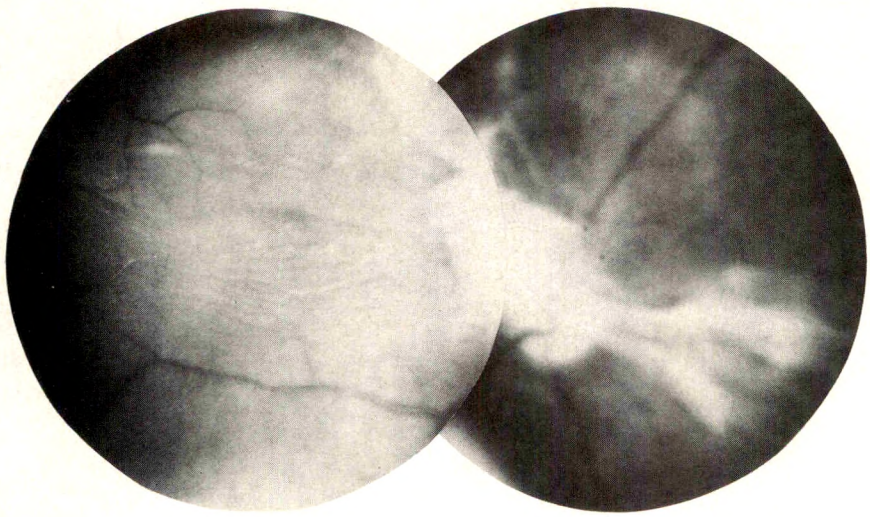


Fig. 4 (Machemer and Williams). Case 2, right eye after second vitrectomy. Traction on the macula is less than that seen preoperatively. Peripapillary membranes have been reduced.

lemmal densities usually characteristic of myofibroblasts were also seen in these surface cells (Fig. 7, bottom right).

Collagen fibers comprised the bulk of the membrane, with a diameter ranging from 2,400 to 3,000 nm (Fig. 8, left). Cells found within the membranes between bundles of collagen fibers were similar to the surface cells, but they lacked microvilli. Smaller cells with round nuclei and prominent rough endoplasmic reticulum were also seen within the membrane, but they lacked intracytoplasmic filaments. These cells were probably fibrocytes. Those membranes that were detached from the retina had cells on both surfaces with similar features.

Membranes from the second procedure were similar to those of the first with regard to type and location of cells. There were two populations of collagen fibers, most commonly those whose diameter was approximately 3,000 nm, and another less common group with a diameter of approximately 1,000 nm (Fig. 8, right). Membranes from the third procedure were more cellular. Spindle-shaped cells were seen within the membranes as well as on the surface of the membranes. Most of these cells exhibited a well-formed basal lamina and intracytoplasmic filaments 800 to 1,000 nm in diameter. Cells that lined a surface of the membrane exhibited microvilli and extended long cytoplasmic processes along the membrane surface. Occasional macrophages and leukocytes were seen on the membrane surface. Some cells within the membrane were degenerating and showed a disor-

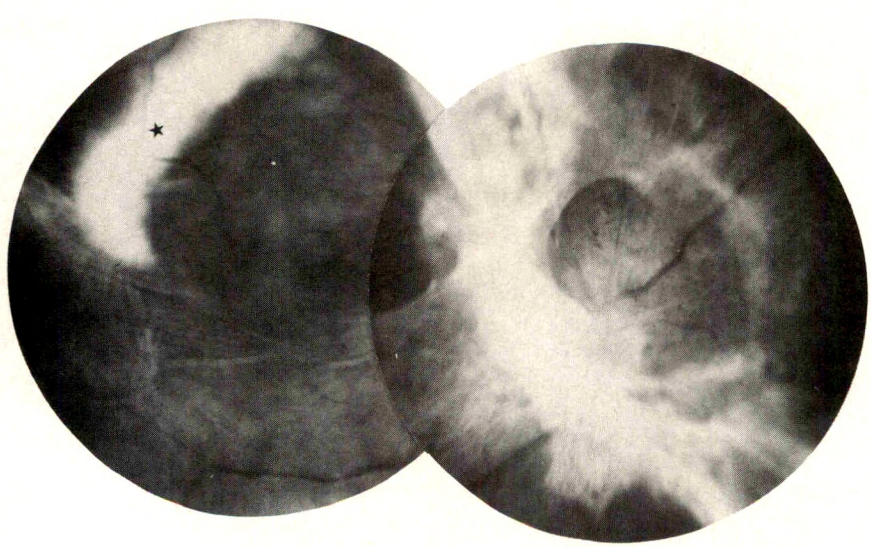


Fig. 5 (Machemer and Williams). Case 2, right eye immediately before third vitrectomy. Note preretinal proliferation and subretinal exudates (asterisk) (compare with Fig. 4).

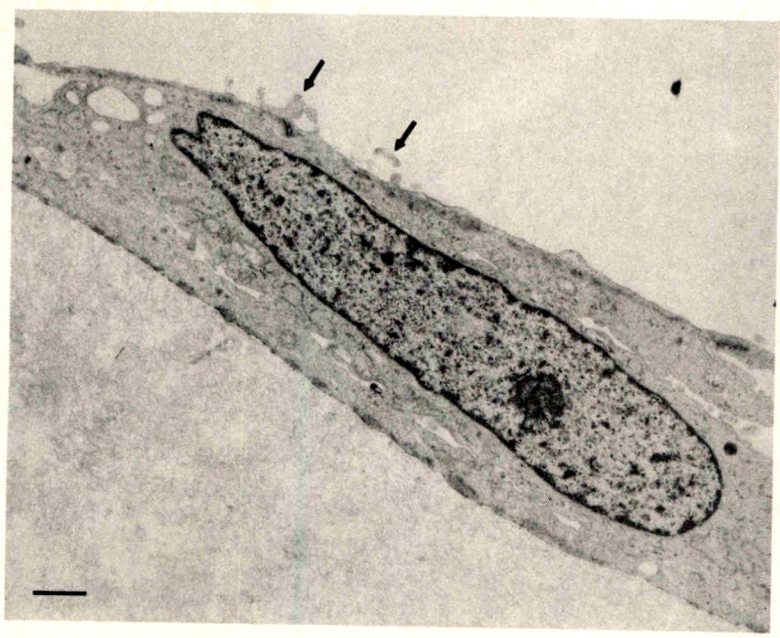


Fig. 6 (Machemer and Williams). Case 2, first vitrectomy. Polarized cell with cytoplasmic processes overlapping from adjacent cells. Note microvilli (arrows) on the surface. There is a suggestion of a basal lamina where the cell rests on a thick layer of collagen (bar = 1 μm).

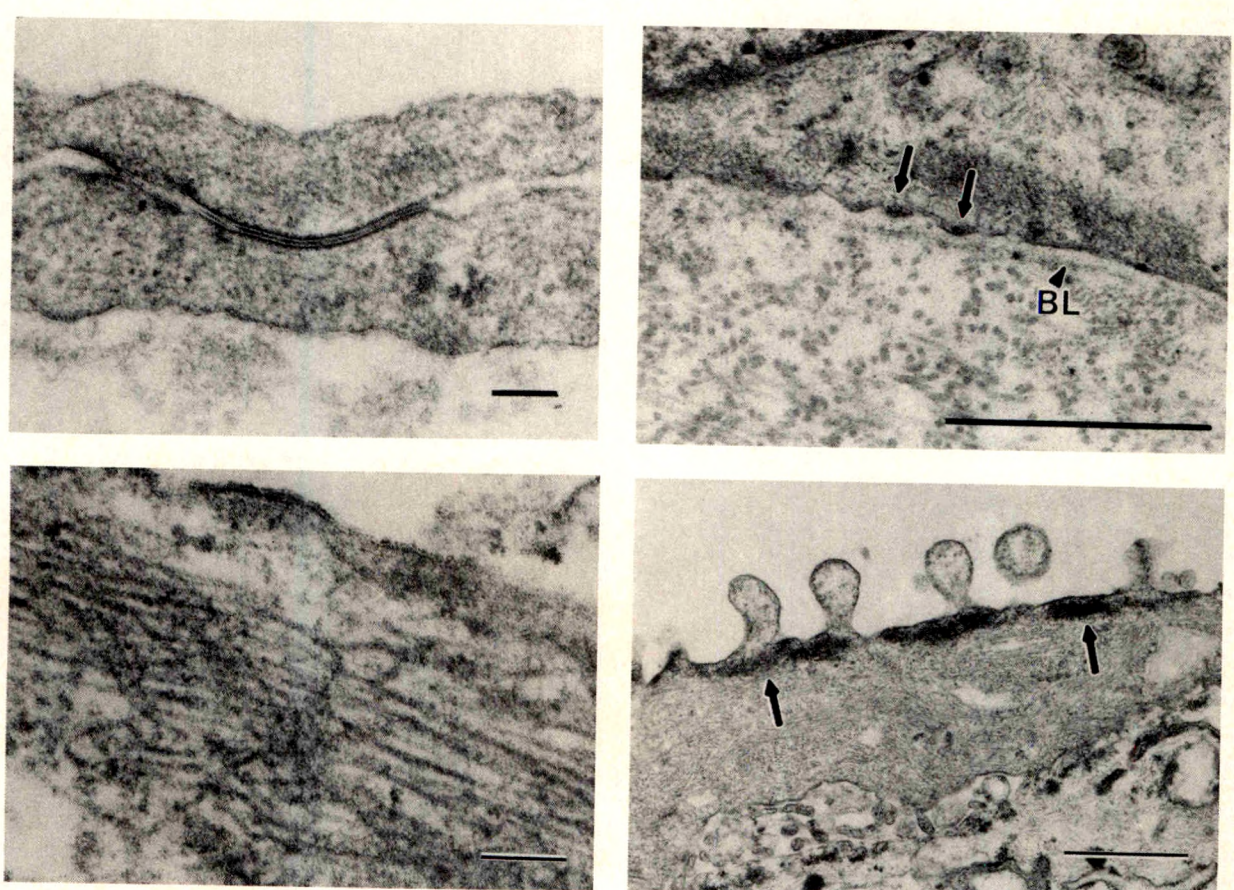


Fig. 7 (Machemer and Williams). Case 2. Top left, Tight junction between adjacent glial processes (bar = 0.1 μm). Top right, Well-formed basal lamina (BL) and hemidesmosomal attachments to the basal lamina (arrows) (bar = 1 μm). Bottom left, Intracytoplasmic filaments, 800 to 1,000 nm in diameter, that are typical for cells of glial origin (bar = 0.1 μm). Bottom right, Fusiform subplasmalemmal densities in a surface cell suggestive of contractile elements usually seen in myofibroblasts (arrows) (bar = 1 μm).

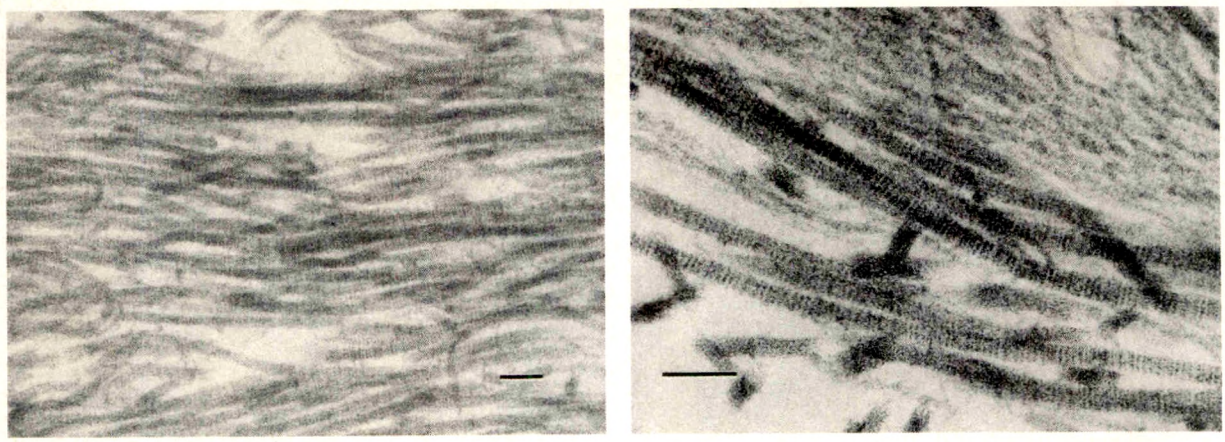


Fig. 8 (Machemer and Williams). Case 2. Left, Newly formed collagen fibers 2,400 to 3,000 nm in diameter (bar = 0.1 μm). Right, Collagen fibers. Note two different populations, 3,000 and 1,000 nm in diameter (bar = 0.1 μm).

ganized nuclear and cytoplasmic architecture. Again, there was a collagenous stroma of the membrane, with fibers that ranged from 2,700 to 3,800 nm in diameter. Remnants of the internal limiting lamina were present on the retinal side of the membrane (Fig. 9). In this case, the membrane had been peeled from the retinal surface. A few sections contained a blood-filled capillary.

Case 3

In January 1975 this 7-year-old girl had a visual acuity of 20/60 in both eyes and a history of recent visual loss. The child was the product of a normal pregnancy and delivery, and there was no history of early visual loss in other family members.

Both eyes showed slight dragging of the vessels toward the temporal side; strands extend-

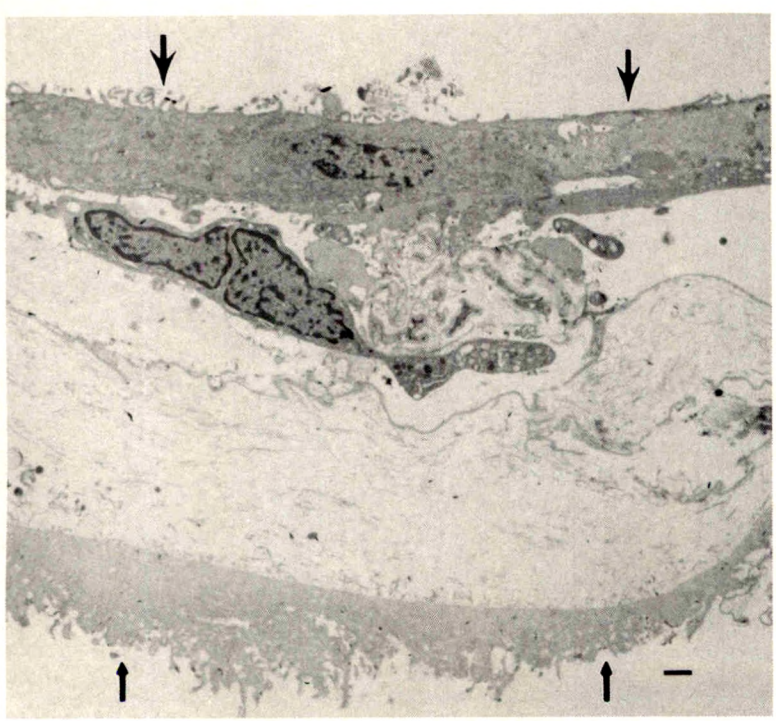


Fig. 9 (Machemer and Williams). Case 2, membrane from third vitrectomy. Retinal glial cell (large arrows) is present on the surface. Internal limiting lamina is visible on the external side of the collagenous membrane. Note leukocyte (small arrows, bar = 1 μm).

ed from the disk to the temporal periphery. The strands were intimately connected to the retina and caused the retina, including the macula, to detach shallowly. In the temporal periphery, vessels showed shunt formation and small dilatations, and ended abruptly slightly anterior to the equator. The retina appeared thickened and of a dull white coloration. Yellow exudates were seen under the detached parts of the retina.

A vitrectomy was performed in the right eye, and the left eye was treated with cryopexy. The membranes were difficult to lyse from the retina. The vascular lesions in the right eye were not treated at this time. Vision improved in both eyes and was good for several years. This child was seen again 7½ years later with a visual acuity of R.E.: 3/200 and L.E.: 20/200. In the right eye, a recurrent detachment had developed. A large number of vitreous veils were seen exerting traction on the retina, and yellow subretinal exudate was found nasally. The left eye also showed a traction band pulling nasal retina across the optic nerve head and elevating temporal and inferior retina, including the macula. Yellow subretinal exudate was seen. The vitrectomy was repeated in the right eye and performed for the first time in the left eye. It was difficult to lyse these membranes from the surface of the retina, especially on the temporal side. The vascular abnormalities were treated this time with cryoapplications and a circumferential buckle was placed in both eyes. Once again, the retina reattached after the operation posterior to the buckle. Dry subretinal yellow deposits remained temporally and inferiorly. Visual acuity remained hand motions in the right eye, but improved to 20/70 in the left eye.

One year later, visual acuity was R.E.: light perception and L.E.: 20/200. The retina in the right eye was attached, with dry subretinal yellow deposits temporally. The left eye appeared quiet, and the superior retina was attached; yellow exudates were found in the inferior periphery extending into the foveal area, with elevation of the inferior retina. Additional cryotherapy of the peripheral vessels was recommended and performed elsewhere.

The patient returned in April 1987 complaining of blurred vision in the left eye for one week. Visual acuity was R.E.: light perception and L.E.: 20/125. Ophthalmoscopy disclosed transvitreal veils posterior to the buckle, which were exerting traction on the nasal retina. Subretinal exudate was present, and an open retinal break was seen superiorly posterior to the buckle. The patient was believed to have a combined traction-rhegmatogenous detachment in the left eye and subsequently underwent a revision of the vitrectomy and scleral buckling procedure. Vascular lesions were treated with intravitreal cryotherapy. Postoperatively, the posterior pole was attached, although some inferotemporal traction elevation of the retina was present.

Histopathologic findings—Specimens obtained from the first vitrectomy on the left eye showed a thick collagen membrane covered with cells, with spindle-shaped nuclei and long cytoplasmic processes that had microvilli. Cells with similar nuclei were occasionally seen within the membranes between multiple layers of collagen fibers. Most of these cells (on the surface and within the membranes) had cytoplasmic microfilaments 800 to 1,000 nm in diameter, and prominent rough endoplasmic reticulum was present in the surface cells. Occasional leukocytes were seen on the surface of the membrane. Collagen fibers in the membranes were approximately 2,400 nm in diameter.

Membranes from the second vitrectomy were similar. In some cases, double layers of glial cells were found on the vitreal side of the membrane surface, and these cells demonstrated prominent microvilli. As seen with scanning electron microscopy, the cells were polygonal, with an epithelial-like appearance (Fig. 10). The undersurface of the membrane was covered by similar-appearing cells. Where the membrane was not covered by cells—presumably where it had been peeled from the retina—collagen bundles were visible. This secondary membrane was more cellular than the membrane removed at the first vitrectomy. Occasional spindle-shaped cells without intracytoplasmic filaments were seen within the membrane. They were probably fibrocytes. Two populations of collagen fibers were present and measured 3,600 to 3,900 nm and 1,100 nm in diameter. These fibers were abundant and comprised the bulk of the membrane.

The second vitrectomy performed on the right eye yielded a specimen that was thicker and more cellular than the membrane from the left eye. Spindle-shaped cells with cytoplasmic microvilli were seen on one surface of the membrane. Multiple cells with similar nuclei were seen within the membrane, some of which extended long cytoplasmic processes. Collagen fibers within the membrane were approximately 2,400 nm in diameter.

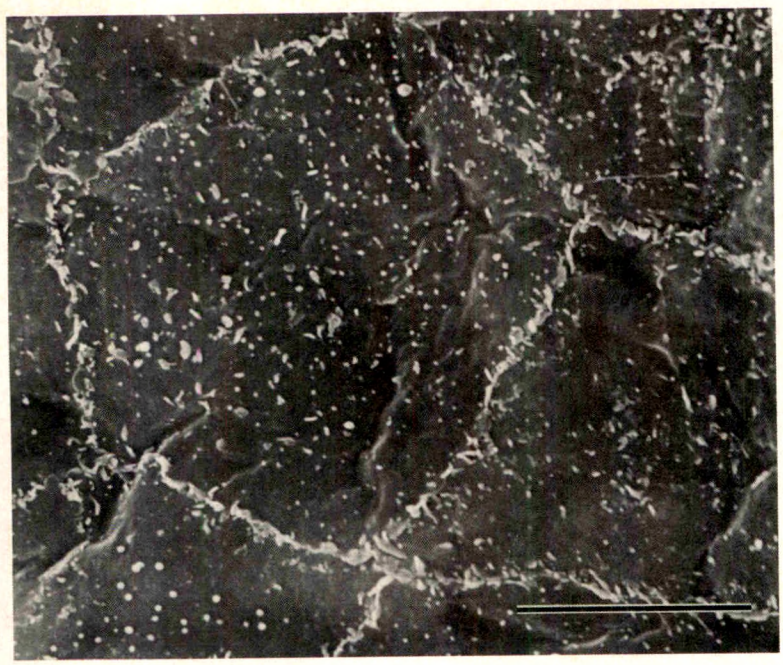


Fig. 10 (Machemer and Williams). Case 3. Scanning electron micrograph of vitreous membrane exhibiting polygonal surface glial cells with microvilli (bar = 1 μm).

Case 4

An 11-year-old girl with a history of congenital retinal lesions in both eyes and a family history of "eye disease" was seen in March 1985 because of decreased vision in her right eye. She was the product of a full-term pregnancy and received no oxygen after birth. Visual acuity was R.E.: 20/40 and L.E.: 20/60. Ophthalmoscopy demonstrated that the vessels of the temporal arcade in the right eye were dragged temporally, and the macular area was slightly folded and shallowly detached. In the periphery, between the 8 and 11 o'clock meridians, yellow subretinal exudate and abnormal-appearing vessels as well as minor hemorrhages were seen. The rest of the fundus periphery appeared normal. In the left eye, the disk, vessels, and macula appeared normal. There was some preretinal glial tissue in the inferior temporal region.

The patient was believed to have familial exudative vitreoretinopathy and amblyopia in the left eye. The patient underwent vitrectomy, removal of a membrane that covered the retina between the disk and the temporal periphery, and cryotherapy to the peripheral vascular abnormalities.

Four months later, visual acuity in the right eye was 4/200, and examination of the fundus disclosed tissue extending from the disk into the vitreous. The peripapillary region was involved in a traction detachment, intravitreal membranes were seen inferiorly, and much yellow subretinal exudate was seen in the temporal periphery. In October 1985 the patient underwent revision of the vitrectomy, membrane peeling, cryotherapy, and a scleral buckling procedure. During the vitrectomy, the material being cut and aspirated appeared to be similar to vitreous, although the vitreous had presumably been removed during the first procedure. In May 1986 visual acuity in the right eye was 4/200. Ophthalmoscopy disclosed that the vitreous cavity was empty, the retina was attached posterior to the buckle, and the exudate had nearly disappeared. No further reproliferation had occurred.

Histopathologic findings—Membranes from the second vitrectomy were available for study with transmission electron microscopy. In this tissue, loosely packed collagen fibers were interspersed with cells that had round and spindle-shaped nuclei. Some of the cells with spindle-shaped nuclei were found on the membrane surface and had microvilli. Many of these cells had intracytoplasmic microfilaments 800 to 1,000 nm in diameter. Occasional macrophages were seen on the membrane. Three populations of collagen were seen, which had diameters of 800 to 1,100 nm, 1,670 to 2,000 nm, and 2,800 to 3,330 nm.

Case 5

An 8-year-old boy examined in April 1979 had a visual acuity of 6/200 in his left eye. The retina was almost totally detached, with exten-

sive subretinal exudates. Inferiorly, there was a dome-shaped lesion with vascular abnormalities. No feeder vessels were seen in this area. A diagnosis of Coats' disease was made, and the lesion was treated with cryotherapy. Three months later, visual acuity and intraocular findings were unchanged. Examination with a contact lens suggested traction on the retina, especially in the area of the inferior, mound-like retinal elevation. A vitrectomy was performed. The vitreous was found to be gelatinous and very adherent to the retina. It was especially solid over the mound. Since not all traction could be released, an encircling band was placed around the eye. The vascular lesion was not treated. Postoperatively, the retina began to slowly reattach, and the subretinal exudate decreased. After 1½ years, the retina was completely reattached, with remnants of dry deposits still visible. There was a densely pigmented scar in the fovea. Visual acuity was 3/200.

Histopathologic findings—This tissue was more cellular than those previously described. Many macrophages and leukocytes were present within it as well as on the membrane surface. Cells with spindle-shaped nuclei and 800- to 1,000-nm intracytoplasmic filaments were present within the membrane and on the membrane surface. Collagen fibers surrounded these cells in a less organized manner than seen in previous specimens. Two populations of collagen fibers were found in approximately equal quantities, those approximately 1,000 nm in diameter and those 2,100 to 2,800 nm in diameter. A few endothelial cells lining vascular channels were seen.

Case 6

A 31-year-old man was seen in January 1984. He was known to have Coats' disease, and he had had decreased vision for an extended period of time in his right eye. He also had had increased intraocular pressure in this eye for several months. On examination visual acuity was light perception. Also noted were heavy flare and cells (3+) in the anterior chamber, posterior synechiae, and a mature cataract. A total retinal detachment was demonstrated on ultrasound. A lentectomy was performed, followed by a vitrectomy, because multiple vitreoretinal traction bands had caused a total traction retinal detachment. Vascular lesions were seen in the temporal periphery but were not treated.

Fifteen months later, the retina was completely reattached, and the exudate had disappeared. Coarse pigmentary changes were seen in the temporal periphery, with no vascular disease visible. Visual acuity had improved to 6/200.

Discussion

Fibrous proliferation into the vitreous cavity because of angiomatosis retinae, exudative vitreoretinopathy, and Coats' syndrome is uncommon. All of our patients developed preretinal and intravitreal membranes and what appeared to be altered vitreous, which exerted traction on the retina. Most of them showed subretinal exudate. Patients 1, 2, 3, and 6 were initially treated with vitreous surgery alone, without treatment of the vascular lesions. Patient 4 had intraoperative cryotherapy and Patient 5 had preoperative cryotherapy. Subretinal exudates decreased after vitrectomy. Patients 1 through 4 showed recurrence of preretinal and vitreous membranes, which necessitated repeat vitreous surgery and treatment of the vascular lesions.

The one common feature in all cases was the vascular abnormality. It is known that von Hippel's disease,[6] angiomatosis retinae,[7,8] and exudative vitreoretinopathy[9] lead to subretinal exudation because of the presence of abnormal vessels. Less known, however, is the tendency of these diseases to lead to vitreous alterations with frank membrane formation.[4,10,11] We believe that the vitreous alterations precede the occurrence of subretinal exudates. As the altered retinal vessels leak through the retina into the vitreous cavity, they release a proteinaceous exudate. As long as the retina is attached, this exudate leaks into the vitreous cavity or into the surrounding retina, resulting in vitreous haze and intraretinal exudate formation. Once a traction retinal detachment occurs, proteinaceous material also leaks into the subretinal space. The pigment epithelium attempts to remove the fluid, but the traction on the retina prevents its total absorption. Protein remains in the subretinal space, slowly accumulates, and thus becomes visible as exudate. This explanation expands previous attempts to provide a pathogenetic mechanism by assuming that detachments of the retina are solely caused by exudation into the subretinal space.[12-14]

Release of retinal traction can be achieved by vitrectomy. This resulted in retinal reattachment with disappearance of the subretinal fluid

in all of our cases. Recurrence of retinal detachment is always combined with renewed strand formation and traction on the retina and not vice versa. Because of this, we initially assumed that performing a vitrectomy alone might be sufficient to eliminate subretinal fluid accumulation (Cases 1, 2, 3, 5, and 6). However, it became apparent that except for Cases 5 and 6, recurrence of proliferation occurred, accompanied by renewed traction detachment. Just as the original proliferations had been stimulated by exudates from the diseased retinal vessels, the recurrent membranes continued to develop because of ongoing exudation. This exudate is probably an excellent culture medium for proliferating cells. Once a membrane has detached itself from the retina a new membrane may form on its surface, resulting ultimately in multiple vitreous sheets and giving the clinical appearance of a nonvitrectomized eye.

Vitrectomy without treatment of the cause, the leaking vessels, is usually temporary and recurrence of subretinal exudation does occur unless diseased vessels are totally destroyed. Even then, recurrences are possible as new vascular disease may develop (for example, in angiomatosis retinae and Coats' syndrome).

Possibly stimulated by the proteinaceous vascular exudate, the vitreous is infiltrated by cells deriving from the retina, which change its consistency by producing collagen and form bands and strands. Typically, these strands consist of collagen and cells that have glial characteristics such as polarity, desmosomal and junctional complexes, and basement membrane formation. Microvilli are seen where there is a free surface of the membrane. Characteristic 800- to 1,000-nm intracytoplasmic filaments identify these cells as being of glial origin.[15-17] The cells may have their origin in small proliferations that break through the internal limiting lamina and initially extend along the retinal surface.[18] Thus, when peeled from the retinal surface, internal limiting lamina may be ripped from the retina. Conspicuously absent from all specimens were retinal pigment epithelial cells, thus confirming that they have no role in the pathogenesis of proliferative retinal vasculopathy.

Collagen was seen in all membranes. Most of the collagen fibers were thicker than 2,000 nm in diameter and thus need to be considered new-formed collagen.[19] The origin of this collagen is probably from glial cells. Collagen has been shown to be synthesized in vivo and in vitro by astrocytic glial cells derived from the rabbit retina.[20] Collagen, 800 to 1,600 nm in diameter, is typical for native vitreous collagen,[21,22] and it was seen in Cases 1 through 5. In Case 1, all the collagen was approximately 1,000 nm in diameter, and the membrane was hypocellular. As this specimen was from a primary vitrectomy, it could represent condensed original vitreous collagen, although the clinical impression of dense, gelatinous vitreous suggests deposition of newly formed collagen. In Cases 2 through 5, mixed populations of collagen were seen. As membranes from Cases 2, 3, and 4 with two populations of collagen fibers were taken during a second vitrectomy, their fibers of approximately 1,000 nm may represent a de novo production of vitreous-like collagen by glial cells or fibrocytes, thus giving the appearance of vitreous regeneration as noted during the vitrectomy revisions in these eyes. Although unlikely, some of the original vitreous may have been left despite careful attempts to remove it during the first vitrectomy.

Membranes, such as those recurring soon after surgery, were more cellular than older membranes. As a membrane matures, the collagen within it becomes more tightly packed and the number of retinal glial cells seems to be reduced. The finding of a large number of glial cells in a membrane indicates clinical activity, whereas older inactive membranes are mainly comprised of collagen fibers.

Contraction of the preretinal strands containing glial cells and collagen seems to lead to auto-stripping of the membrane from the retinal surface in some places. The resulting detached membrane has two surfaces, a vitreal and a retinal surface. The latter is probably covered by cells originating from the vitreal surface, thus explaining the similarity of the cells on the two sides of the membrane. Where the membrane was peeled directly from the retinal surface, it shared either uncovered collagen or internal limiting lamina.

The described late stages of these various retinal vasculopathies seem to form a distinct pathologic picture. All retinal vascular diseases that result in retinal detachment and are known to cause subretinal exudates belong to this entity (angiomatosis retinae, familial exudative vitreoretinopathy, Coats' syndrome, and retinopathy of prematurity).

This entity has probably remained unknown because, unless severe disease has developed, most cases are simply overlooked. In our own practice, we now find vitreous disease in most vasculopathies with so-called exudative detachments. It is apparent that only few cases

have to be treated with vitreous surgery. Usually exudation stops after treatment of the vascular lesion. Vitreous surgery and treatment of the vascular lesion should be considered in cases where subretinal exudates develop and where there is vitreous membrane formation with strong traction on the retina that keeps the retina detached.

ACKNOWLEDGMENT

Patient 6 was examined by Michael Lambert, M.D., Department of Ophthalmology, U.S.A.F. Medical Center, San Antonio.

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OPHTHALMIC MINIATURE

Mrs. Pugh: Then it's time to get up. Give me my glasses.
No, not my *reading* glasses, I want to look *out*.
I want to see.

Dylan Thomas, *Under Milk Wood*
J. M. Dent, 1954

HLA Typing in Birdshot Chorioretinopathy

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We examined 49 patients with birdshot chorioretinopathy in whom HLA typing had been performed. Of these 49 patients, 47 (95.9%) had the HLA-A29 antigen. The HLA-B12 (B44) antigen was also significantly associated with the disease, but this antigen is known to be in linkage disequilibrium with the antigen HLA-A29. The HLA-A2 antigen was less frequent in patients with birdshot chorioretinopathy than in the control group of normal European individuals (20% as compared to 44.6%).

THE CLINICAL MANIFESTATIONS of birdshot chorioretinopathy were first described and defined as a separate ocular entity in 1980 by Ryan and Maumenee.[1] In a recent study of a large group of European patients with birdshot chorioretinopathy, the importance of the different clinical manifestations and their diagnostic value were assessed.[2] In 1982 Nussenblatt and associates[3] found that birdshot chorioretinopathy was strongly associated with the gene coding for the major histocompatibility complex antigen HLA-A29. Of 20 birdshot chorioretinopathy patients studied by these investigators, 80% were shown to carry the HLA-A29 antigen.

We undertook this study to confirm the association between HLA-A29 and birdshot chorioretinopathy in a large group of European patients, and its potential value as a major diagnostic criterion for birdshot chorioretinopathy.

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Subjects and Methods

Between 1985 and 1986, birdshot chorioretinopathy was diagnosed in 102 patients according to the following criteria, which were based on the clinical manifestations as described by Ryan and Maumenee[1]: (1) the typical fundus picture of symmetrically scattered, small, cream-colored flecks, (2) retinal vasculopathy, with leakage of large retinal vessels, cystoid macular edema, or both, (3) disk edema or optic atrophy, and (4) inflammatory signs in the vitreous. Data on HLA-A29 typing performed in local tissue typing centers were obtained in 49 patients with birdshot chorioretinopathy, including 26 Belgian, 17 Dutch, five French, and one English patient. Complete HLA-A and -B typing was available in 45 patients.

Control subjects included 183 uveitis patients from The Netherlands and Belgium[4]; 3,924 healthy subjects from HLA-typing studies in The Netherlands[5] and Belgium (data from the Bloodtransfusion Centre, Department of Haematology, University of Gent); and 2,650 healthy subjects from Europe.[6] Observations on the linkage disequilibrium between certain haplotypes were also used for comparison.[7]

Statistical evaluation of the data included homogeneity testing of the group (chi squared), the relative risk factor, and Fisher's exact test. We used the methods described by Mathews[8] concerning the statistical aspects of immunogenetic associations with diseases. For determining the relative risk factor in the case of small numbers, we used a modified formula according to Haldane as described in the work of Svejgaard.[9] The statistical significance was determined by the one-sided Fisher's exact test.

Results

Complete HLA-A and -B typing data were available in 45 patients with birdshot chorioret-

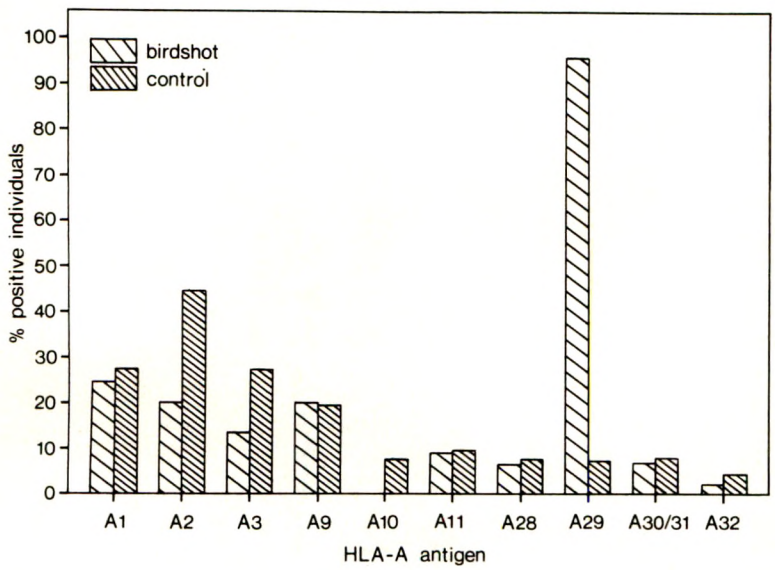


Figure (Priem and associates). HLA-A antigen frequencies in birdshot chorioretinopathy.

inopathy. HLA-A29 was present in 43 of these patients (95.6%). HLA-B12 was present in 29 patients (64.4%), all of whom were also HLA-A29 positive. Comparison of the HLA antigen frequencies of these patients with those of the 3,924 healthy Dutch and Belgian controls showed a significant association with the antigen HLA-A29 (P corrected $< 1.10^{-45}$) and HLA-B12 (P corrected $< 1.10^{-10}$) in the birdshot chorioretinopathy patients. A much lower frequency of the HLA-A2 antigen was found in the patient group as compared to this control group (Figure). Similar results were found when the patient group was compared to the group of 2,650 European controls.

The strong association between HLA-A29 and birdshot chorioretinopathy can also be seen from the high relative risk factor of 224.35 (Table 1). Additionally, the relative risk that an HLA-B12-positive individual will acquire birdshot chorioretinopathy is 7.08 times higher than that of an individual lacking this antigen. Because HLA-A29 and -B12 are known to be in linkage disequilibrium, we compared the simultaneous occurrence of A29 and B12 in birdshot chorioretinopathy patients and in controls. No significant difference was found (Table 2). Of the 29 A29- and B12-positive patients, 28 carried the B44 subtype and one the B45 subtype of B12.

Data concerning only HLA-A29 were available in 49 patients with birdshot chorioretinopathy. Of these 49, 47 were HLA-A29 positive (95.9%), whereas only 13 of 183 control patients with uveitis (7%) carried this antigen (Table 3).

TABLE 1
RESULTS OF HLA TYPING

HLA ANTIGEN	PHENOTYPE FREQUENCY (%) PATIENTS (N = 45)	CONTROLS* (N = 3,924)	χ^2	RELATIVE RISK	FISHER'S P
A1	24.4	27.2	.18	.89	.7257
A2	20.0	44.6	10.93	.32	.9998
A3	13.3	27.2	4.32	.44	.9917
A9	20.0	19.4	.01	1.08	.5195
A10	0.0	7.7	3.74	.13	1.0000
A11	8.9	9.6	.02	1.02	.6354
A28	6.7	7.6	.05	1.00	.6749
A29	95.6	7.2	462.13	224.35	.0000
A30 + 31	6.7	7.7	.07	.99	.6838
A32	2.2	3.9	.35	.82	.8371
B5	6.7	12.3	1.32	.59	.9268
B7	22.2	21.6	.01	1.07	.5195
B8	31.1	19.7	3.66	1.88	.0475
B12	64.4	20.2	53.23	7.08	.0000
B13	2.2	3.8	.32	.84	.8292
B14	4.4	4.1	.02	1.36	.5511
B15	6.7	15.0	2.44	.47	.9732
B16	0.0	5.3	2.53	.19	.9999
B17	0.0	6.3	3.02	.16	.9999
B18	15.6	5.9	7.45	3.12	.0160
B21	4.4	2.1	1.11	2.61	.2548
B22	6.7	4.2	.67	1.87	.2967
B27	4.4	10.0	1.55	.51	.9481
B35	11.1	13.4	.19	.88	.7353
B37	0.0	3.1	1.44	.34	.9999
B40	8.9	10.8	.17	.89	.7326

*Healthy subjects from Belgium and The Netherlands.

TABLE 2
FREQUENCY OF HLA-A29 AND HLA-B12

SUBJECTS	A29 AND B12 POSITIVE	A29 POSITIVE AND B12 NEGATIVE	TOTAL NO. OF SUBJECTS
Birdshot chorioretinopathy patients	29	14	43
Healthy subjects[7]	124	114	238

TABLE 3
FREQUENCY OF HLA-A29 IN PATIENTS WITH BIRDSHOT CHORIORETINOPATHY AND CONTROLS WITH UVEITIS

SUBJECTS	A29		TOTAL NO. OF PATIENTS
	POSITIVE	NEGATIVE	
Birdshot chorioretinopathy patients	47	2	49
Uveitis patients	13	170	183

Contrary to the findings of Nussenblatt and associates,[3] we found one patient with birdshot chorioretinopathy who was both A29-and B27-positive. Furthermore, one of the HLA-A29-negative patients was also B27-positive.

Discussion

Our findings confirm the strong association between birdshot chorioretinopathy and the HLA-A29 antigen. The risk that an HLA-A29-positive individual might acquire birdshot chorioretinopathy is approximately 200 times higher than it would be for a person not carrying this antigen. This association is presently the strongest HLA class I disease association reported; the HLA-B27 association with ankylosing spondylitis has a relative risk of 69.1 in whites.[10] Other weaker HLA-A29 disease associations have also been reported for carcinoma of the liver (relative risk, 3.1), porphyria cutanea tarda (relative risk, 2.47), recurrent herpes labialis (relative risk, 3.0), and subacute sclerosing panencephalitis (relative risk, 3.61).[10]

The strong association found in the present study may be the result of the strict criteria used for the diagnosis of birdshot chorioretinopathy. In addition to the clinical criteria currently used, future diagnostic criteria may include HLA-A29 typing. Although over 100 European patients with birdshot chorioretinopathy were examined clinically,[2] data on HLA typing were only available in 49 patients, including all the Dutch and Belgian patients and a limited number of French and English patients.

The association between birdshot chorioretinopathy and HLA-A29 may provide clues concerning the origin of this disease. Of the various HLA-disease associations previously described, most have been associated with HLA-DR and HLA-B antigens; few associations have been described with the HLA-A locus.[10] Thus, the HLA-A29 birdshot chorioretinopathy association is unique in this respect.

The finding that HLA-A2 appears less frequently in birdshot chorioretinopathy patients than in the normal population is probably secondary to the finding that almost all patients carry the HLA-A29 antigen. An increase of one antigen results in the decrease of one or more of the other antigens belonging to the same locus.

It is now becoming clear that genes within the HLA system play an important role in the regulation of T-cell function. HLA class I genes (HLA-A, -B, or -C) regulate antigen presentation to helper T cells. In general, it is assumed that the involvement of HLA genes reflects host responses to infectious agents. Exceptions include enzymatic deficiencies such as the 21-hydroxylase deficiency, which maps within the HLA regions.[9,10]

Various hypotheses have been proposed to explain the direct involvement of the HLA system in the pathogenesis of certain diseases.[11] These include the following: (1) failure of infectious agents to associate with HLA antigens, (2) gaps in the repertoire of T-cell recognition of antigens, which is influenced by the HLA genes, (3) molecular mimicry, whereby HLA antigens resemble infectious agents resulting in tolerance, and (4) HLA antigens that may act as more or less efficient receptors for infectious agents.

Although exact mechanisms have not yet been proven, both experimental evidence and

recent data concerning infectious disease in humans point to the following general scheme. Infectious agents may be the initial trigger for many of the HLA-associated diseases, whereby the immune response genes within this complex, in concert with other genes, will influence the resulting immune response. Depending on the host-parasite relationship, disease could either be caused by the chronicity of the infection or by the secondary initiation of autoimmune reactions.

Clinical evidence suggests that birdshot chorioretinopathy is an inflammatory condition in which secondary autoimmune reactions directed against ocular tissue antigens may be involved.[3] No clinical clues are as yet available concerning a possible role of certain infectious agents in these patients. The identification of a disease susceptibility gene may, however, be the first step toward discovering the pathogenesis of birdshot chorioretinopathy.

Acknowledgment

P. Verbeke, Ph.D., Department of Statistics, University of Gent, performed the statistical analysis.

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Ophthalmic miniature

He could not say that he liked to paint. It was neither pleasure nor relief, it was self-torture, but somehow, that didn't matter. He sat on a canvas stool before a small easel and he looked at an empty sweep of hills, at the woods and the sky. He had a quiet pain as sole conception of what he wanted to express, a humble, unbearable tenderness for the sight of the earth around him—and something tight, paralyzed, as sole means to express it. He went on. He tried. He looked at his canvases and knew that nothing was captured in their childish crudeness. It did not matter. No one was to see them.

Ayn Rand, *The Fountainhead*
New York, The Bobbs-Merrill Company, 1971, p. 565

The Diagnosis and Treatment of Bilateral Masked Superior Oblique Palsy

Burton J. Kushner, M.D.

I reviewed retrospectively the records of 147 consecutive patients who had superior oblique palsy. Of the 147 patients, 28 had bilateral superior oblique palsies, and in nine of the 28 the involvement was so asymmetric that the palsy in the lesser affected eye was either completely masked or almost masked preoperatively. Relying on preoperative diagnostic criteria such as the presence of bilateral objective torsion, cover testing in the oblique fields of gaze, size of the subjective cyclotropia, amount of the "V" shift, and subjective symptoms, all nine patients underwent bilateral surgery at the time of their initial operation and obtained satisfactory results. No patient was later found to have bilateral masked superior oblique palsy after unilateral surgery.

SUPERIOR OBLIQUE PALSY has been described as the most common form of vertical paralytic strabismus.[1] It frequently occurs bilaterally. Scott and Kraft[2] reported a 29% incidence of bilaterality in a large series of patients with superior oblique palsy. Urist[3] described two cases of bilateral superior oblique palsy that were so asymmetric that the paresis of the lesser affected eye was completely hidden by the large hypertropia of the more affected eye until after unilateral surgery was performed. Since then, others have reported this phenomenon and the term "masked bilateral superior oblique palsy" has been popularized to describe this entity.[4-7] The frequency of bilateral masked superior oblique palsy in these reports ranged between 8% and 28% of patients thought to have unilateral superior oblique palsy preoperatively. Jampolsky[8] stated that the examiner should always assume that a paresis is bilateral until it is proven to be otherwise. Any degree of positive forced tilt to both sides indicates bilaterality; that is, a large degree of right hyper on right tilt and perhaps only one to two prism diopters of left hyper on left tilt, is sufficient for a bilateral diagnosis.

In their classification and treatment protocol for bilateral superior oblique palsy, Scott and Kraft[2] described treatment recommendations for asymmetric bilateral superior oblique palsy. They did not, however, give surgical recommendations for suspected bilateral masked superior oblique palsy. Despite Jampolsky's admonition, as far as I can determine, there are no published guidelines for treating bilateral masked superior oblique palsy if it is recognized preoperatively.

Since 1974 my approach to the surgical treatment of superior oblique palsy has included considering bilateral surgery if I suspected a bilateral masked problem on clinical grounds preoperatively. The purpose of this review was to determine if this approach has been successful in decreasing the frequency of bilateral masked superior oblique palsy requiring a second operation.

Material and Methods

The records of all patients seen by me at the University of Wisconsin Pediatric Eye Clinic or the Davis-Duehr Eye Clinic with the diagnosis of bilateral or unilateral superior oblique palsy between 1974 and 1986 were reviewed retrospectively. The diagnosis of superior oblique palsy was made primarily by the Parks three-step test,[9] with consideration being given to other clinical conditions that mimic superior oblique palsy on the three-step test.[10] When possible, measurements were also performed in the oblique fields of gaze, and at least a subjective cover test was performed in all of the

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oblique fields to rule out a reversal of the hypertropia.

In cooperative patients the double Maddox rod test was used to assess subjective torsion, and since 1975 the presence of objective torsion was noted. Because in patients with normal ocular motility the fovea occupies a position that lies on the same level as the lower half of the disk, I considered any eye in which the fovea was below the lower margin of the disk as exhibiting objective extorsion. This observation was determined by using indirect ophthalmoscopy while the eye being studied fixated on the dimmed light of the indirect ophthalmoscope. Because the indirect ophthalmoscope produces an inverted image, objective extorsion appeared to be represented by the fovea lying above the superior disk margin. In many cases fundus photography was used to aid in this clinical assessment. This method of assessing objective extorsion has been previously described.[11]

If the eye that was not the hypertropic eye in the primary position showed a hypertropic deviation in any field of gaze, including the oblique fields, or on ipsilateral head tilt, a diagnosis of bilateral superior oblique palsy was made. Because the three-step test, which is commonly used to diagnose superior oblique palsy, does not require oblique field measurements, it may not successfully detect bilateral asymmetric superior oblique palsy if the hypertropia of the lesser affected eye is only present in the oblique fields. In these cases, the bilaterality of the palsy is not truly masked. For this reason I use the term "almost masked" to describe this clinical situation. The term masked bilateral superior oblique palsy is reserved for those patients in whom a hypertropia of the lesser affected eye is not present in any field of gaze nor on head tilt. Patients were included in the statistical analysis if follow-up was for at least six months after surgery, or one year from the time of initial diagnosis if the patients did not undergo surgery.

I suspected bilateral masked superior oblique palsy if the subjective cyclotropia was greater than 10 degrees, if the "V" shift (difference in horizontal alignment between upgaze and downgaze) was greater than 20 prism diopters, if there was a small hypertropia in the primary position with a large hypertropia of the same eye in adduction, if a chin down rather than a head tilt posture was assumed, or if objective torsion was present bilaterally. In cases in which a composite of these clinical findings suggested bilaterality, asymmetric bilateral surgery was performed.

Although the surgical procedures used in such patients were determined individually based on their motility pattern, there were several underlying principles used consistently. If the deviation was greater in upgaze than downgaze, typically bilateral asymmetric inferior oblique weakening procedures were performed. This was accomplished by recessing the inferior oblique 6 mm in the eye that was hypotropic in the primary position, and recessing the inferior oblique 10 or 12 mm in the eye that was hypertropic in the primary position preoperatively. A 10-mm recession was performed if the inferior oblique had an overaction of +1 or +2 preoperatively, and a 12-mm recession was performed if the overaction was +3 or +4.

If the deviation was greater in downgaze, typically bilateral asymmetric superior oblique tightening procedures were performed, either bilateral asymmetric superior oblique tucks or a superior oblique tuck combined with a Harada-Ito procedure in the other eye. Bilateral asymmetric superior oblique tucks were accomplished by first tucking the superior oblique in the hypertropic eye an amount that was just sufficient to produce tightness of the tendon intraoperatively while the tucking device was being expanded. The amount of the tuck was then measured. The superior oblique tendon in the hypotropic eye was then tucked either half that amount, if the hypertropia in the primary position was under 6 prism diopters, or three-fourths that amount, if the hypertropia in the primary position was between 6 and 12 prism diopters preoperatively. If the vertical deviation in the primary position was so large that it could not be corrected with asymmetric oblique surgery alone (typically greater than 12 prism diopters), I added a recession of the inferior rectus muscle in the hypotropic eye unless the superior rectus muscle in the hypertropic eye was found to be contractured with intraoperative forced duction testing. If contracture was found, then the superior rectus muscle in the hypertropic eye was recessed. An adjustable suture was used if possible. During postoperative adjustment an attempt was made to adjust the ocular alignment to orthophoria in the primary position, provided that this did not produce an overcorrection in the downgaze reading position. If such an overcorrection were produced, I readjusted the ocular alignment to produce orthophoria in the downgaze reading

position, leaving a small residual undercorrection in the primary position.

My criteria for evaluating the surgical success in bilateral masked and almost masked superior oblique palsy was as follows. If postoperatively the patient did not require prisms to be free of diplopia in the primary position at distance, at near (including the downgaze reading position), and up to 20 degrees right or left of primary, without an abnormal head posture, I rated the outcome as "excellent." I graded the outcome as "good" if all of the above criteria were met except that the patient required some prism ground in his or her spectacles. The rating of "good" was withheld, however, if the amount of prism required could not be ground into spectacles and the use of a Fresnel lens was needed (typically greater than a total of five prism diopters for the right and left eyes combined). If a different amount of prism was needed for distance than at the near downgaze reading position, and the patient required separate spectacles for distance and reading, the outcome was considered "fair." Any patient not meeting all of the above criteria or requiring a Fresnel lens on a long-term basis was considered to have a "poor" outcome.

I use the term congenital superior oblique palsy to describe patients in whom the cause was unclear, documented to be long-standing, but not necessarily diagnosed in infancy. Patients in whom previous vertical muscle surgery confused the diagnosis of superior oblique palsy were eliminated from this analysis.

Results

This series consisted of 147 consecutive patients with the diagnosis of superior oblique palsy. Of these 147 patients, 96 had congenital unilateral superior oblique palsy (Table 1). The cause in the five patients listed as "other" in Table 1 included one case each of central nervous system tumor, meningitis, and herpes zoster and two cases were iatrogenic.

I did not perform surgery on 35 of the 147 patients (Table 2). A surprising number of patients had relatively mild symptoms, which either did not require treatment or could be managed with a small amount of vertical prism. Those patients who did not undergo surgery were free of diplopia in the primary position or in the downgaze reading position, except during times of extreme fatigue. They had to be free of a cosmetically unacceptable head posture to maintain fusion. The mean follow-up period for these patients was 2.9 years (S.D. = 2.0 years). As expected, patients with unilateral superior oblique palsy who did not require surgical intervention had a much smaller deviation in the primary position (mean = 7.17 prism diopters; S.D. = 4.8 prism diopters) than patients with unilateral superior oblique palsy who did require surgery (mean = 18.7 prism diopters; S.D. = 10.18 prism diopters). This difference was significant (t-test, $P < .001$).

TABLE 1
DISTRIBUTION OF CASES OF SUPERIOR OBLIQUE PALSY BY CAUSE
(N = 147)

TYPE	CONGENITAL	TRAUMATIC	OTHER
Unilateral	96	18	5
Bilateral*	5	14	0
Bilateral almost masked†	3	2	0
Bilateral masked‡	2	2	0
Total	106	36	5

*Bilateral hypertropias seen on three-step test.
†Hypertropia of lesser involved eye only seen in oblique fields.
‡Hypertropia of lesser involved eye not seen.

TABLE 2
REASONS FOR NOT OPERATING ON PATIENTS WITH SUPERIOR OBLIQUE PALSY
(N = 35)

	CAUSE*	
REASON	CONGENITAL	TRAUMA
Unilateral		
Mild problem†	15	1
Surgery performed elsewhere	4	1
Recovered‡	0	4
Surgery advised, patient refused	1	1
Lost to follow-up	0	1
Bilateral		
Mild problem†	0	1
Surgery performed elsewhere	0	2
Recovered‡	0	2
Lost to follow-up	0	1
Total	20	14

*The patient with unilateral superior oblique palsy caused by herpes zoster also had a mild problem.
†May have needed prisms for single binocular vision.
‡Recovery sufficient that surgery was not needed.

TABLE 3
CLINICAL CHARACTERISTICS OF BILATERAL AS COMPARED TO UNILATERAL SUPERIOR OBLIQUE PALSY

CHARACTERISTIC	UNILATERAL	BILATERAL	P VALUE
Trauma as cause	8 of 119 (15%)	18 of 28 (64%)	P<.001*
Mean ± S.D. difference in hyper on tilt right and left (Δ)	24.32 ± 7.8	12.2 ± 11	P<.01†
Excyclotropia by double Maddox rod test (deg)	7.0 ± 4.5	13.63 ± 7.1	P<.01†
"V" shift (Δ)	2.0 ± 4.6	13.9 ± 11	P<.001†

*By chi square test.
†By *t*-test.

Clinically, patients with bilateral superior oblique palsy were more likely to have trauma as a cause, had larger excyclotropias and "V" shifts, but smaller forced head tilt differences than patients with unilateral superior oblique palsy (Table 3). For the purpose of statistical analysis, the difference recorded between the hypertropia on right and left head tilt was in terms of absolute numbers. For example, if a patient had a 15-prism diopter right hypertropia on right tilt and a 10-prism diopter left hypertropia on left tilt, the difference would be recorded as 25 prism diopters. Excyclotropia was recorded as the sum of the total of the excyclotropia seen in both eyes with the double Maddox rod test. The "V" shift represented the difference in the horizontal alignment between upgaze and downgaze, as described by Kraft and Scott.[7]

Five patients were considered to have almost masked bilateral superior oblique palsy and four patients were thought to have masked superior oblique palsy. Their preoperative prism and cover test measurements, and objective and subjective cyclotropia, are represented in Figures 1 and 2 and their clinical course is outlined in Table 4.

None of the 90 patients on whom surgery was performed for suspected unilateral superior oblique palsy later showed evidence of a masked superior oblique palsy in the fellow eye. In one additional patient seen in consultation I suspected a bilateral masked superior oblique palsy based on the criteria outlined above. Although I recommended that the patient undergo bilateral surgery, he subsequently underwent unilateral surgery by the referring ophthalmologist. Several weeks after surgery he was found to have a previously masked superior oblique palsy in the fellow eye.

Discussion

Many authors believe that bilaterality of superior oblique palsy can be predicted based on the presence of a large "V" shift, greater than 12 degrees of subjective excyclotropia, and a chin down posture preoperatively.[12-15] Others, however, have reported cases of bilateral masked superior oblique palsy that did not show these findings preoperatively.[6,7] Although in this series the bilaterally affected patients had more subjective torsion, a greater "V" shift, and more frequently a history of trauma as the causative factor, bilaterality could not always be diagnosed by these criteria alone. Many of the patients with bilateral involvement did not show these findings.

Assessing the oblique fields of gaze was essential in diagnosing bilaterality. Although accurate prism and cover testing in the four oblique fields can be technically difficult, a qualitative cover test should be performed in those fields of gaze to look for a reversal of the hypertropia. Often there is a moderate horizontal deviation present in the field of the inferior obliques, which may mask a small vertical deviation. Neutralization of the horizontal deviation with prisms while performing a cover test is helpful in visualizing small vertical deviations in the range of 2 to 4 prism diopters. One should add to Jampolsky's admonition[8] that the presence of a reversal of hypertropia in any field of gaze, including the oblique fields, and not only on opposite head tilt, is diagnostic of a bilateral superior oblique palsy. I believe that some of the previously reported bilateral masked superior oblique palsies were really almost masked, and the examiner failed to check the oblique fields of gaze. Hugonnier[4] was probably describing bilateral almost masked superior oblique palsy when he stated that a suspicion (of bilaterality) should be aroused if there is even mild overaction of the inferior oblique in the hypotropic eye.

Although Scott and Kraft's[2] classification of bilateral superior oblique palsy does include a category for patients with marked asymmetry of involvement, I believe that the bilateral al-

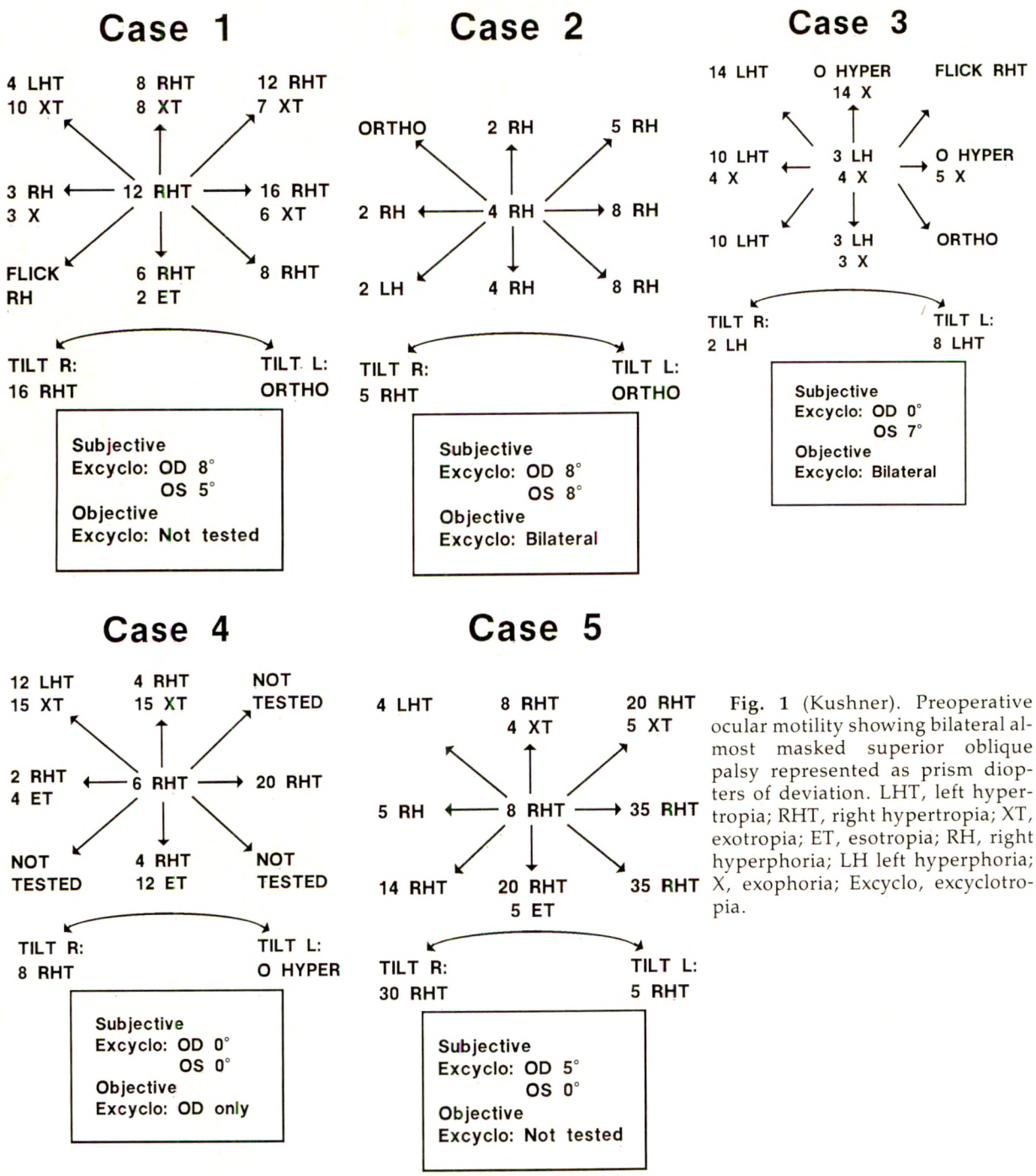


Fig. 1 (Kushner). Preoperative ocular motility showing bilateral almost masked superior oblique palsy represented as prism diopters of deviation. LHT, left hypertropia; RHT, right hypertropia; XT, exotropia; ET, esotropia; RH, right hyperphoria; LH left hyperphoria; X, exophoria; Excyclo, excyclotropia.

most masked superior oblique palsy should be thought of as a separate category. Because the stated diagnostic criteria for their series did not include oblique field measurements (even though they were performed for many of their patients), their classification system as written may not diagnose the almost masked bilateral patient.

Kraft and Scott[7] suggested that increased use of objective tools, such as the observation of fundus torsion, may help separate masked bilateral superior oblique palsy from truly unilat-

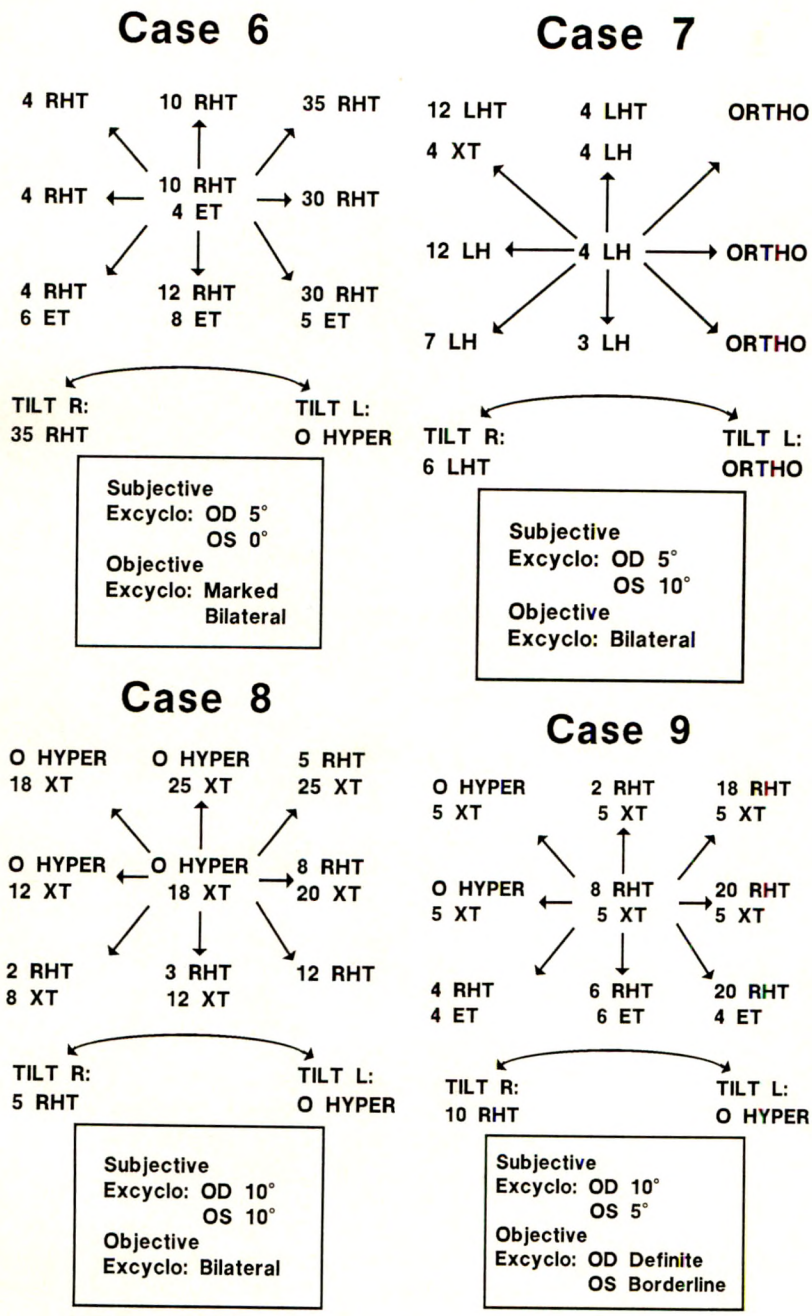


Fig. 2 (Kushner). Preoperative ocular motility. Bilateral masked superior oblique palsy was diagnosed preoperatively.

eral cases. I have found this to be a helpful diagnostic tool. In some of the patients in this series it was the main finding suggesting bilaterality. The presence of a small hypertropia in the primary position (under 5 prism diopters) and a large hypertropia when the hypertropic eye was adducted was also a helpful sign.

The data confirmed my clinical impression that patients with bilateral superior oblique palsy show a smaller difference in the hypertropia between right and left head tilt than patients with unilateral superior oblique palsy. This is contrary to what one might assume. In the hypothetical situation of a right superior oblique palsy, a large right hypertropia on right tilt and a small right hypertropia on left tilt are typically seen. If upon that a left superior

TABLE 4
CLINICAL COURSE OF BILATERAL MASKED AND ALMOST MASKED SUPERIOR OBLIQUE PALSY

PATIENT NO., SEX, AGE AT SURGERY (YRS)	SURGICAL PROCEDURE	OUTCOME	FOLLOW-UP (MOS)
1, F, 57	Recess right inferior oblique 10 mm, recess left inferior oblique 6 mm, recess left inferior rectus 3 mm*	Good	26
2, M, 56	Harado-Ito procedure bilaterally	Excellent	32
3, F, 16	Recess right inferior oblique 6 mm, recess left inferior oblique 10 mm	Excellent	16
4, F, 42	Recess right inferior oblique 12 mm, recess left inferior oblique 6 mm	Good	18
5, M, 20	Tuck right superior oblique, Harada-Ito procedure left superior oblique	Excellent	38
6, M, 41	Recess right inferior oblique 12 mm, recess left inferior oblique 6 mm, recess left inferior rectus 3 mm*	—	—
7, F, 14	Recess right inferior oblique 6 mm, recess left inferior oblique 10 mm	Excellent	13
8, M, 32	Harada-Ito procedure bilaterally, recess left lateral rectus 7 mm*	Good	—
9, M, 49	Tuck right superior oblique, Harada-Ito procedure left superior oblique	Excellent	47

*Adjustable suture used.

oblique palsy, which should have a large left hypertropia on left tilt and a small left hypertropia on right tilt, is superimposed, the hypertropias should be approximately additive. This apparent discrepancy can be explained. Typically, a patient with a unilateral superior oblique palsy fixes with the uninvolved eye, so there is no alteration in the normal resting tonus to that eye in the primary position. If a patient has a bilateral superior oblique palsy, the fixing eye by definition is one with a paresis of a depressor. Therefore, more innervation than usual must be sent to the inferior rectus muscle to keep the eye in the primary position. This excessive "downgaze" innervation should be accompanied by an inhibition of the superior rectus muscle (Sherrington's law). This relative inhibition of the superior rectus muscle may interact with the stimulation of the superior rectus muscle on ipsilateral head tilt, resulting in less elevation of the eye (Fig. 3). This same process explains why a bilateral asymmetric superior oblique palsy may be masked and not show a reversing hypertropia on head tilt right and left. If the superior rectus muscle is inhibited in the lesser involved eye because of excessive innervation to the inferior rectus muscle, the superior rectus muscle is less likely to raise the eye sufficiently to cause a reversal of the hypotropia (Fig. 4).

Souzas-Dias[5] offered a different hypothesis for the masking of the superior oblique palsy in the lesser involved eye. He theorized that the superior rectus muscle in the more affected eye will overact (contracture), producing an underaction of the inferior rectus muscle on the same side. The underaction of the inferior rectus muscle will result in a greater innervation to the superior oblique in the lesser involved eye, which negates the underaction caused by the paresis and avoids development of overaction of its antagonist, the inferior oblique. This increased innervation to the superior oblique in the lesser involved eye hides the paresis.

In order for Souza-Dias' explanation to be valid, however, the patient would have to be fixing with the eye with the greater degree of superior oblique involvement. If a patient does not fixate with the hypertropic eye, as is usually the case, there would be no increased innervation necessary to the inferior rectus muscle in the hypertropic eye, and therefore no increased innervation to its yoke muscle, the superior oblique in the lesser involved eye.

In the present series, nine of the 112 patients (8%) who underwent stabismus surgery had either a bilateral masked or bilateral almost masked problem, and all were diagnosed as having bilateral involvement preoperatively. This is virtually identical to the incidence of bilateral masked superior oblique palsy reported by Kraft and Scott[7] in their large series.

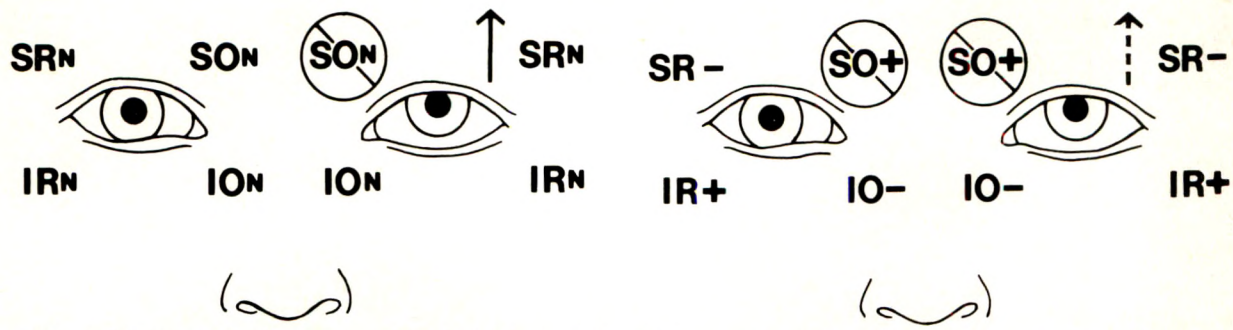


Fig. 3 (Kushner). Left, In a hypothetical left superior oblique palsy there is no change in the innervational tonus to the extraocular muscles in the primary position if fixation is carried out with the uninvolved right eye. Right, In a hypothetical bilateral asymmetric superior oblique palsy with greater involvement in the left eye than the right eye, there is a change in the normal resting tonus in the primary position. If fixation is carried out with the lesser involved right eye, in order to bring the right eye to the primary position there is a stimulation of the depressors (superior oblique and inferior rectus muscles) and an inhibition of the elevators (inferior oblique and superior rectus muscles). Because the superior oblique is paretic, more of this increased depression action will be coming from the inferior rectus muscle. Because the fixing eye determines the neural input to the nonfixing eye, there will also be stimulation of the left superior oblique and left inferior rectus muscles, with inhibition of the left inferior oblique and left superior rectus muscles. This relative inhibition of the left superior rectus muscle results in less left hypertropia than in the unilateral case. SR, superior rectus muscle; SO, superior oblique muscle; IR, inferior rectus muscle; IO, inferior oblique muscle; n, normal resting tonus; +, stimulation above normal resting tonus; −, inhibition.

Although appropriate awareness of the signs of bilateral masked involvement can substantially decrease the frequency of second surgical procedures, bilaterality cannot always be detected preoperatively. Many of the previously reported cases of bilateral masked superior oblique palsy would have been misdiagnosed using the criteria I used in this series.[3,4,7] The one preoperative diagnostic criterion used throughout this series that has not been reported previously was the observation of bilateral objective fundus torsion. This may be an important factor in diagnosing bilaterality, as had been predicted by Kraft and Scott.[7]

Surgical principles similar to those used in this series for treating bilateral almost masked superior oblique palsy were used by Pinchoff, Bergstrom, and Sandall[15] for treating two pa-

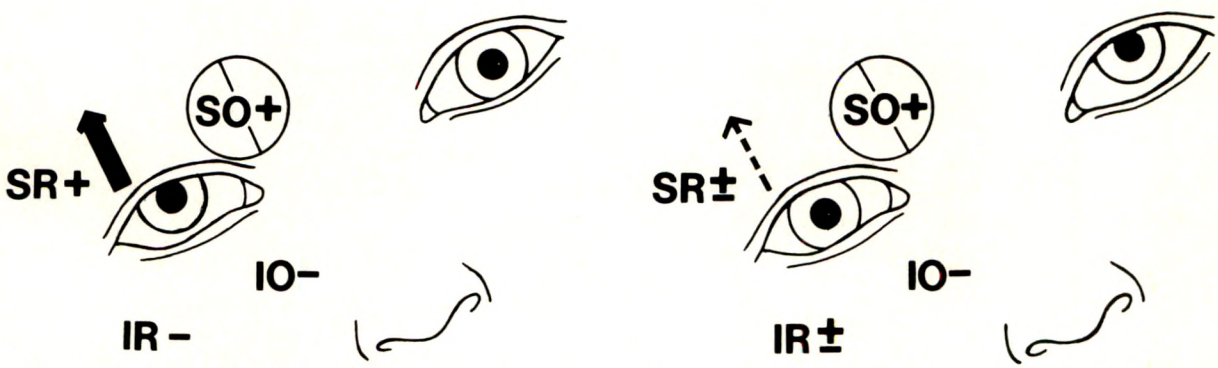


Fig. 4 (Kushner). Left, In hypothetical right superior oblique palsy on head tilt right, the superior rectus and superior oblique muscles are innervated and the inferior oblique is inhibited. Because the superior oblique is paretic, the innervation to the superior rectus muscle causes the eye to elevate. Right, In hypothetical bilateral superior oblique palsy with lesser involvement of, but fixation with, the right eye, the right inferior rectus muscle is innervated to bring the eye to the primary position. This innervation for depression causes partial inhibition of the superior rectus muscle. This, in part, negates the reflex for innervation to the right superior rectus muscle that occurs because of the right head tilt. This results in less elevation of the right eye.

tients with similar motility patterns. These two cases combined with those reported here suggest that markedly asymmetric bilateral superior oblique palsy can be effectively treated with bilateral asymmetric surgery. Bilateral asymmetric surgery can also be safely performed in patients in whom a bilateral masked superior oblique palsy is suspected, despite there being no manifestation of hypertropia of the eye with lesser involvement.

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OPHTHALMIC MINIATURE

" . . . Ten years ago a pair of these glasses ab oculis ad legendum were sold for six Bolognese crowns. I was given a pair of them by a great master, Salvinus of the Armati, more than ten years ago, and I have jealously preserved them all this time, as if they were—as they now are—a part of my very body."

"I hope you will allow me to examine them one of these days. I would be happy to produce some similar ones," Nicholas said, with emotion.

"Of course," William agreed, "but mind you, the thickness of the glass must vary according to the eye it is to serve, and you must test many of these lenses, trying them on the person until the suitable thickness is found."

Umberto Eco, *The Name of the Rose*
Translated by William Weaver
New York, Harcourt Brace Jovanovich, 1983, p. 86

Bacillus Keratitis Associated With Contaminated Contact Lens Care Systems

Paul B. Donzis, M.D., Bartly J. Mondino, M.D., and Barry A. Weissman, O.D.

We examined two soft contact lens wearers who developed keratitis associated with *Bacillus* contamination of their contact lens care systems. Patient 1 developed a corneal ulcer caused by *B. subtilis*, and Patient 2 demonstrated multiple, diffuse, punctate corneal epithelial opacities associated with *B. cereus* contamination in the contact lens and lens case compartment. The contact lens cases of both patients contained *Bacillus* spores that survived multiple heat disinfection treatments. Three different contact lens chemical disinfection systems used for the minimum recommended time failed to kill the *Bacillus* organisms.

MICROBIAL CONTAMINATION of contact lens cases or solutions may be an important source of microorganisms that cause corneal ulcers in contact lens wearers.[1] Chemical or heat disinfection will kill most microorganisms present in contaminated care systems. *Acanthamoeba* organisms, which cause devastating corneal infections in contact lens wearers, may resist chemical and peroxide disinfection and are only consistently killed by heat.[2] *Bacillus* organisms, which also cause corneal ulcers in contact lens wearers,[3,4] are able to form spores that resist heat.[5] Herein we describe two soft contact lens wearers who developed keratitis associated with *Bacillus* contamination of their contact lens care systems. These organisms resisted both heat and chemical contact lens disinfection systems.

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Case Reports

Case 1

A 19-year-old woman used daily-wear soft contact lenses for two years without difficulties. Each night she removed her lenses and rinsed them with thimerosal-preserved saline. She then placed the lenses in her contact lens case. She disinfected her lenses with heat once or twice each week. She replaced the saline in her case every two to three days, but never rinsed or air-dried her case.

Two days before examination, she developed a red, painful left eye. On examination best corrected visual acuity was R.E.: 20/20 and L.E.: 20/30. Results of slit-lamp examination of her right eye were normal. Her left eye showed conjunctival hyperemia and edema. The left cornea had a peripheral anterior stromal infiltrate approximately 2 mm in diameter, with an overlying epithelial defect that was 0.5 mm in diameter. The anterior chamber showed 3+ cells and flare. A few keratic precipitates were also present. A diagnosis of microbial keratitis was made. Scrapings of the corneal ulcer were sent for culture and Gram stain. Her contact lens case and solutions were also cultured. A regimen of fortified topical cefazolin and gentamicin hourly was begun, and her corneal ulcer gradually healed over the next five days. *Bacillus subtilis* was grown from both contact lens case compartments and the corneal ulcer.

On examination one month later, best corrected visual acuity in the left eye was 20/20. A superficial anterior stromal scar was present in the area of the previous ulcer. She resumed wearing her soft contact lenses using heat disinfection and was instructed in proper care. Four months later, cultures of her care system were free from microbial contamination.

Case 2

A 27-year-old woman had used daily-wear soft contact lenses for ten years without experiencing any problems. She disinfected her lens-

es with heat three to four times each week using homemade saline prepared from distilled water and salt tablets. Each batch of homemade saline lasted four to six weeks. One week before examination, she noticed the onset of redness and irritation in her left eye but continued to wear her lens. Over the next two days, vision in the left eye began to deteriorate and the eye became painful and photophobic. She was examined by her ophthalmologist who noted corneal epithelial opacities, stopped her contact lens use, and started a regimen of topical prednisolone sodium phosphate-sulfacetamide sodium eyedrops. When her condition did not improve over the next few days, she was referred to our institution.

Best corrected visual acuity was R.E.: 20/20 and L.E.: 20/40. Conjunctival hyperemia was noted in the left eye. In the left cornea were multiple, diffuse, punctate epithelial opacities that stained with fluorescein (Figure). Results of ophthalmoscopy were normal. The right eye was normal. Laboratory investigation showed growth of *B. cereus* from the solution in the left lens compartment of her contact lens case and her homemade saline. The left contact lens, which had been stored in a separate container since its removal from the eye, also grew *B. cereus*. The right lens and right lens compartment in her case showed no bacterial growth.

She was treated with topical gentamicin four times daily, and the epithelial lesions disappeared over the next six days. Her best corrected visual acuity improved to 20/20. Three weeks after our initial examination, the patient was fit with new contact lenses and instructed in proper care. She is doing well using heat disinfection on a daily basis. Results of repeat cultures of her care system were negative for microbial contamination.

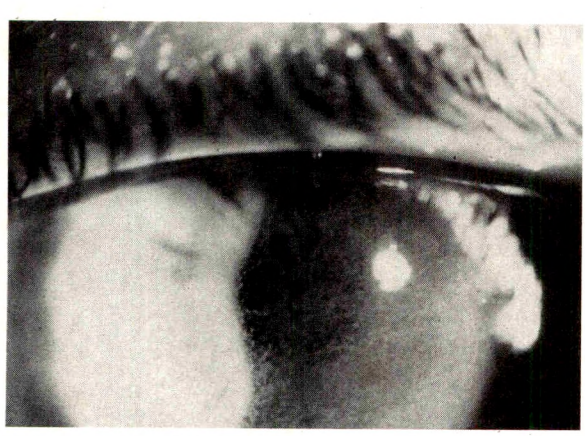


Figure (Donzis, Mondino, and Weissman). Left cornea of Patient 2 showing multiple, diffuse, epithelial opacities.

Material and Methods

A pure subculture of *B. subtilis* isolated from the cornea of Patient 1 and a pure subculture of *B. cereus* obtained from the contact lens case of Patient 2 were obtained on 5% sheep blood agar plates. A suspension of each organism was made in sterile normal saline at a concentration of approximately 1×10^6 colony-forming units per milliliter. Gram stain demonstrated the presence of spores as well as vegetative bacterial forms. One milliliter of each suspension was then placed into one compartment of ten sterile contact lens cases. A suspension of *Staphylococcus epidermidis* at approximately the same concentration as the *Bacillus* organisms was placed in the other compartment as a control. The cases were then placed in new heat disinfection units and subjected to a complete heat disinfection cycle. We also subjected the contaminated contact lens cases of our two patients to five consecutive heat disinfection cycles using new heat disinfecting units. After the disinfection cycle was complete, cultures were taken of each compartment. The cases were carefully opened so as not to touch the interior, and a sterile cotton swab was used to culture the solution inside the case. The cultures were streaked immediately on 5% sheep blood agar plates, which were then incubated at 37 C for 24 hours.

Suspensions of *B. cereus*, *B. subtilis*, and *S. epidermidis*, at a concentration of approximately 1×10^6 colony-forming units per milliliter, were also made in the following chemical disinfecting solutions: polyaminopropyl biguanide, thimerosal-chlorhexidine, and 3% hydrogen peroxide. Five samples of each organism were tested for each solution. Cultures were taken using a sterile cotton swab after four hours (minimum recommended time) and 24 hours of incubation in the first two solutions and after ten minutes (minimum recommended time) and five hours of incubation in the peroxide solution. All cultures were streaked on 5% sheep blood agar plates, which were incubated at 37 C for 24 hours.

Results

In all heat-disinfected cases, the compartment with *B. cereus* or *B. subtilis* showed growth

of the organism. The compartment inoculated with *S. epidermidis* showed no growth.

Growth of *B. cereus* or *B. subtilis* was present after five and 24 hours of incubation in either polyaminopropyl biguanide or thimerosal-chlorhexidine. Growth of *B. cereus* or *B. subtilis* was noted after ten minutes but not after five hours of incubation in hydrogen peroxide. *Staphylococcus epidermidis* was consistently killed at all incubation times using the chemical disinfecting agents.

Discussion

Our two patients demonstrated *Bacillus* contamination of contact lens care systems associated with corneal disease. Our first patient developed a corneal ulcer caused by *B. subtilis*. In this patient, both sides of the contact lens case were contaminated with this organism. Our second patient showed corneal epithelial opacities that stained with fluorescein. In this patient, *B. cereus* contamination was present only in the contact lens and lens case compartment corresponding to the affected eye. There are several possible causes for the corneal lesions in our second patient. It is doubtful that they represent multiple sites of *B. cereus* infection. Rather, they may represent a hypersensitivity reaction to *B. cereus* antigens or a reaction to the toxins produced by the organism. Endotoxin, for example, has been implicated in the development of noninfectious ring-shaped keratitis in a contact lens wearer whose contact lens and lens case were contaminated with *Pseudomonas aeruginosa*.[6]

Bacillus organisms are a rare but serious cause of endophthalmitis and corneal ulcers.[7,8] *Bacillus cereus*, in particular, has emerged as one of the most virulent organisms to affect the eye. One possible mechanism for its toxicity is the enterotoxin produced by the organism. There are reports of corneal ulcers caused by *Bacillus* organisms with and without the use of soft contact lenses.[3,4,8] In one study, 3% of contact lens-associated corneal ulcers were caused by *Bacillus* organisms.[3]

Bacillus organisms have been found in the contact lens care systems of 3.4% to 7% of asymptomatic patients[9,10] as well as in four of 12 bottles of homemade saline.[9] These organisms form spores that are resistant to heat and many types of chemical disinfectants, and exposure to a temperature of 121 C for 15 minutes or longer may be required to kill them.[5] Thus, once a care system is contaminated, the organism may be difficult or even impossible to eradicate from the system using recommended lens care techniques.

The lens cases of both of our patients contained heat-resistant spores that survived five consecutive heat disinfection cycles. Furthermore, incubation for the minimum recommended time with three different chemical systems failed to kill the *Bacillus* organisms. Only prolonged exposure to 3% hydrogen peroxide effectively eradicated both *Bacillus* species in our study. Hydrogen peroxide has been reported to be sporicidal to *Bacillus* organisms with sufficient exposure.[11]

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Effects of Gentamicin on Healing of Transdifferentiating Conjunctival Epithelium in Rabbit Eyes

Eduardo Alfonso, M.D., Kenneth R. Kenyon, M.D., Donald J. D'Amico, M.D., Amanda M. Saulenas, B.S., and Daniel M. Albert, M.D.

We examined the effects of commercially prepared gentamicin, a wide-spectrum topical antibiotic, on the healing of epithelial defects of the rabbit cornea. Abrasions were created by: (1) removing the corneal epithelium and 3 mm of the conjunctival epithelium (Group 1); and (2) producing the same initial trauma and subsequently removing the central 8 mm of epithelium 28 days after initial healing (Group 2). The complete healing of the large corneal and conjunctival epithelial defects was not delayed when gentamicin solution was used four times a day (Group 1). When the healed epithelium was reinjured while transdifferentiating from conjunctival to corneal epithelium (day 28, Group 2), treatment with the gentamicin solution and its vehicle, both containing benzalkonium chloride, delayed epithelial healing significantly compared with treatment with saline ($P < .01$).

TOPICALLY ADMINISTERED aminoglycoside antibiotics, which are used in the prevention and treatment of ocular infections, are known to have both ocular and systemic side effects.[1,2] Of the drugs in this class, gentamicin, which inhibits normal protein synthesis in susceptible microorganisms, is most commonly prescribed.[3] All available formulations of gentamicin eyedrops contain the preservative benzalkonium chloride, which has been shown to delay corneal epithelial wound healing.[4] Previous studies have not shown any adverse effects of commercially prepared gentamicin on the healing rates of corneal epithelial wounds in rabbits,[5] although the healing rates with gentamicin were slower as compared to those with 5% cefazolin.[6] Morphologic studies describe accumulation of gentamicin in the lysosomes of the conjunctival epithelium,[7] but these lysosomal inclusions have not been reported in corneal epithelium.

In many clinical situations, such as chemical injuries, the conjunctival epithelium is essential for the corneal wound healing process. After healing, the conjunctival epithelium must transdifferentiate into corneal epithelium and can develop surface breakdown that results in new and persistent corneal epithelial defects.[8] Gentamicin is often used as a prophylactic antibiotic in these situations, although its effects on corneal epithelial wound healing from transdifferentiating conjunctival epithelium have not been investigated.

The purpose of this study was to examine the effects of topical gentamicin on the ability of the bulbar conjunctival epithelium to reepithelialize the cornea in rabbits.

Material and Methods

We used 2- to 3-kg New Zealand white female rabbits. All animals were treated in accordance with the Association for Research in Vision and Ophthalmology resolution on the use of animals in research. Rabbits were anesthetized with intramuscular injections of a solution of xylazine (20 mg/kg of body weight) and ketamine hydrochloride (100 mg/kg of body

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From the Howe Laboratory (Drs. Alfonso, D'Amico, and Albert and Ms. Saulenas) and Cornea Service (Drs. Alfonso and Kenyon), Massachusetts Eye and Ear Infirmary, Department of Ophthalmology, Harvard Medical School; and the Cornea Research Unit (Dr. Kenyon), Eye Research Institute, Boston, Massachusetts. This study was supported in part by National Institutes of Health grants EY05769 (Dr. Alfonso), EY03967 and EY05799 (Dr. Kenyon), and EY04474 (Dr. D'Amico); by the National Society to Prevent Blindness; and by the Heed/Knapp Foundation (Dr. Alfonso, 1984–1986).

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weight), in a ratio of 1:1 by volume. Topical proparacaine was applied to the eyes. Slit-lamp examination was performed to rule out preexisting corneal abnormalities.

Group 1—Globes were proptosed, and n-heptanol was applied for 30 seconds with a cotton-tipped applicator to the entire corneal epithelium and to a 3-mm-wide ring of limbal and bulbar conjunctival epithelium of both eyes. The eyes were irrigated thoroughly with 0.9% saline as described previously.[9] The defect was stained with Richardson's stain to confirm the complete removal of the epithelium. Residual stain was removed by repeated washings.

Group 2—The same initial trauma was produced in Group 2 eyes as had been produced in Group 1 eyes. Twenty-eight days after the initial removal of the corneal and conjunctival epithelium, a second epithelial wound was produced by gently scraping off the central 8 mm of corneal epithelium with a scalpel blade. Complete epithelial removal was confirmed by staining the denuded area with Richardson's stain.

Four times a day, at 7:00 A.M., 11:00 A.M., 2:00 P.M., and 5:00 P.M., both eyes of each rabbit received one drop of either commercially available gentamicin sulfate, the drug vehicle (0.1 mg/ml of buffered saline and benzalkonium chloride), saline, or no treatment. This protocol was started on day 1 of primary conjunctival and corneal epithelial removal (Group 1) and continued until complete healing was achieved for the secondary central corneal epithelial removal (Group 2).

All eyes were examined daily for the presence of epithelial defects, vascularization of the stroma, and infection. On day 27 after the initial corneal and conjunctival epithelial removal, eyes were classified into vascularized and nonvascularized groups based on the following criteria: (1) vascularized, vessels extending more than 3 mm beyond the corneoscleral limbus and involving three or more quadrants of the cornea; (2) nonvascularized, vessels extending less than 2 mm onto the cornea and involving no more than two quadrants.

To analyze healing rates, corneal epithelial defects were stained with 2% fluorescein solution. The day of complete closure of the defect was recorded for Group 1. For Group 2, the photographic slides taken at zero, 12, 24, 30, 48, and 54 hours were projected at a standardized magnification and traced with an image analyzer. The rate of wound closure was determined by measuring the area of the wound over time. The means were compared by a two-tailed *t*-test.

On the day when the primary conjunctival and corneal epithelial defect was completely healed (Group 1), randomly selected animals from each treatment group were killed with an overdose of pentobarbital, and the eyes were enucleated. The anterior portion of each globe, consisting of the cornea and a 4-mm ring of sclera and conjunctiva, was removed. The tissue was fixed in 10% buffered formalin, dehydrated, and embedded in paraffin. Sections 6 μm thick were stained with hematoxylin and eosin and periodic acid-Schiff. The total number of epithelial cellular nuclei over a 0.35-mm object length within the central cornea was counted under light microscopy. The number of epithelial cell layers and the presence of stromal vessels and goblet cells were noted.

Results

By day 3, the conjunctival epithelium had passed the periphery of the cornea in all animals in Group 1. Among the eyes that received gentamicin or the vehicle, an average of eight days was required to complete reepithelialization (Table 1). Although eyes receiving no treatment and eyes receiving saline eyedrops healed on the average after seven days, there was no significant difference ($P > .01$) in the number of days required for total healing between eyes treated with gentamicin and the other treatment groups (vehicle, saline, and no treatment).

In Group 2 eyes, all defects closed between 54 and 72 hours. There was no statistical differ-

TABLE 1
DAYS TO TOTAL HEALING AFTER INITIAL CORNEAL AND CONJUNCTIVAL EPITHELIAL REMOVAL (GROUP 1)*

TREATMENT	NO. OF EYES	DAYS (MEAN ± S.D.)
Gentamicin	15	8.13 ± 1.25
Vehicle	13	8.07 ± 0.95
Saline	6	7.66 ± 0.49
No treatment	6	7.00 ± 0.57

*P>.01 by *t*-test comparison between the groups.

TABLE 2
HEALING RATES OF TRANSDIFFERENTIATING CORNEAL EPITHELIUM FROM 8-MM WOUND (GROUP 2)*

TREATMENT	NO. OF EYES	HEALING RATE (MEAN ± S.D.) (MM^2/HR)
Gentamicin	14	1.10 ± 0.14
Vehicle	13	1.14 ± 0.13
Saline	6	1.36 ± 0.11
No treatment	4	1.13 ± 0.15

*Differences between saline and gentamicin groups and saline and vehicle groups was significant at P≤.01.

ence in the average number of hours to total healing between the different treatment groups. Healing rates for the 8-mm central defects were calculated by linear regression from data at zero, 12, 24, 30, 48, and 54 hours. Unlike healing of the initial defect, the second defect in eyes receiving gentamicin, vehicle, or no treatment healed significantly more slowly than those receiving saline ($P < .01$) (Table 2).

In analyzing the effects of vascularization on mean healing rates in each treatment group, no significant difference ($P > .01$) in the healing rates was found in any of the treatment groups, or between vascularized and nonvascularized corneas (Table 3).

After healing of the primary corneal and conjunctival epithelial defects (Group 1), light microscopy of the gentamicin-treated eyes did not show a statistically significant difference ($P > .05$) in the number of epithelial cells in the central cornea compared with vehicle and untreated eyes. Similarly, there was no statistically significant difference ($P > .05$) in the number of cell layers between these groups (Table 4). Goblet cells were present at the corneal periphery in all eyes, and more centrally in eyes with vascularization.

Discussion

Several reports have addressed the effects of topical antibiotics on the healing of 7.3- and 8.0-mm corneal epithelial wounds by the adjacent corneal and limbal epithelium.[5,6] These studies have not shown a statistically significant decrease in the healing rates of corneal epithelium when exposed to gentamicin sulfate

TABLE 3
HEALING RATES FOR TRANSDIFFERENTIATING CORNEAL EPITHELIUM FROM 8-MM WOUND (GROUP 2) IN VASCULARIZED AND NONVASCULARIZED CORNEAS*

TREATMENT GROUP	NO. OF EYES	HEALING RATE (MEAN ± S.D.) (MM^2/HR)
Gentamicin		
Vascularized	6	1.04 ± 0.17
Nonvascularized	7	1.17 ± 0.08
Vehicle		
Vascularized	6	1.12 ± 0.17
Nonvascularized	5	1.17 ± 0.08
Saline		
Vascularized	2	1.45 ± 0.11
Nonvascularized	4	1.31 ± 0.09
No treatment		
Vascularized	2	1.00 ± 0.15
Nonvascularized	2	1.22 ± 0.01
All groups		
Vascularized	16	1.12 ± 0.20
Nonvascularized	18	1.21 ± 0.09

*Comparison between vascularized and nonvascularized corneas in each treatment group was not significant (P>.01); comparison between vascularized plus gentamicin and nonvascularized plus saline was significant at P<.01; comparison between all groups vascularized and all groups nonvascularized was not significant (P>.01).

in its commercially available preparation (3 mg/ml) and in fortified preparations (10 and 14 mg/ml).

Our study evaluated the effects of commercially available gentamicin sulfate drops (3 mg/ml) on the healing of corneal epithelial defects by transdifferentiating conjunctival epithelium. In contrast to the previous studies,[5,6] we removed all the corneal and limbal epitheli-

TABLE 4
LIGHT MICROSCOPIC FINDINGS IN CENTRAL CORNEA ONE DAY AFTER COMPLETE HEALING OF WOUNDS PRODUCED BY REMOVAL OF TOTAL CORNEAL PLUS 3 MM OF CONJUNCTIVAL EPITHELIUM (GROUP 1)

TREATMENT	NO. OF EYES	NO. OF EPITHELIAL CELLS PER HIGH-POWER FIELD (MEAN ± S.D.)	NO. OF EPITHELIAL CELL LAYERS (MEAN ± S.D.)
Gentamicin	6	96.6 ± 21.6	2.7 ± 0.5
Vehicle	4	79.7 ± 51.9	3.5 ± 2.1

um and 3 mm of conjunctival epithelium. This experimental model resembles clinical situations in which total corneal and limbal epithelial loss is followed by resurfacing of the cornea by epithelium derived from the conjunctiva. In these situations, a topical, wide-spectrum antibiotic such as gentamicin sulfate (3 mg/ml) is often prescribed in an average dose of four drops a day to prevent the possibility of corneal stromal infection.[10] This study failed to show a statistically significant difference in the number of days required for complete healing between eyes treated with gentamicin and the control groups (Group 1). However, a trend toward earlier healing was observed in eyes receiving saline or no treatment. Thus, if the clinical situation demands the use of a broad-spectrum prophylactic antibiotic such as gentamicin, the risk of delaying epithelial wound healing appears to be small.

Healing of the corneal surface by conjunctival epithelium requires not only migration but also transdifferentiation, which is often accompanied by irregular resurfacing, vascularization, and poor adhesion to the stroma, with recurrent breakdown and persistent epithelial defects. In our model (Group 2), we produced a secondary 8-mm corneal epithelial defect on day 28, when the transdifferentiating process was at its midpoint.[9] The second epithelial wounding was designed to mimic clinical situations of epithelial breakdown and persistent epithelial defects. The effects of commercially available gentamicin sulfate (3 mg/ml) on corneal epithelial wound healing have not been previously reported for this situation. The delay in healing of the second abrasion was significant not only between gentamicin- and saline-treated eyes, but also between the vehicle- and saline-treated eyes. The group that received no treatment also had a slower healing rate, which may have been a spurious event. Both the commercially prepared gentamicin and the vehicle contain benzalkonium chloride, which has been shown to adversely affect rabbit corneal epithelial wound healing.[4] Since there was no difference in healing rates between the gentamicin- and vehicle-treated eyes, delay in transdifferentiating epithelial healing may have been caused by toxic effects of the benzalkonium chloride and not by the antibiotic. If the antibiotic alone had delayed wound healing, eyes treated with commercially prepared gentamicin would have healed slower than eyes treated with vehicle.

Since all commercially available topical drops of antibiotic solutions contain benzalkonium chloride,[11] the use of these solutions will likely lead to a delay in epithelial wound healing in clinical situations that resemble this animal model. Perhaps the use of nonpreserved antibiotic solutions would be preferable in these situations. Girard[12] described clinically this form of toxicity in postkeratoplasty patients as a superficial punctate keratitis with less precorneal tear film, followed by sloughing of the epithelium.

Corneas that become vascularized after complete epithelial removal appear to resurface, with epithelium abundant in goblet cells, and retain the morphologic characteristics of conjunctival epithelium.[13,14] In this study, we compared epithelial wound healing in vascularized and nonvascularized corneas. Following an 8-mm secondary corneal epithelial defect, epithelial wound healing rates were not statistically different in vascularized and nonvascularized corneas.

Light microscopic examination did not disclose any untoward effects in the eyes treated with gentamicin. These results agree with those of recent studies by Petroutsos and associates,[5] who reported an epithelium three to four layers thick having a comparable mean number of epithelial cell nuclei per 3.5 mm of histologic preparation.

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OPHTHALMIC MINIATURE

For a while he had had fears that nothing in the world existed—at least for him—except by contact. He had first noticed this in his apartment a few days after total blindness, and had dropped a coin, and had not been able to find it anywhere on the floor where it should or might have been; but he had heard it run: yes, run on the hard floor, and even strike something perhaps metallic, and stagger and fall. It was the running that had filled him with anxiety and helplessness: the perversity: the coin had run, and there was no way to tell which way or how far. It lay beyond him; or it lay nowhere.

James Dickey, *Alnilam*
Garden City, New York, Doubleday & Company, Inc., 1987, p. 66

Absence of *Chlamydia* in Trachomatous Lacrimal Sacs

Charles D. Rice, M.D., and Robert C. Kersten, M.D.

We performed lacrimal sac biopsies in 35 patients who underwent dacryocystorhinostomies in Saudi Arabia. The nasolacrimal duct obstructions were presumably secondary to trachoma in 22 cases and unknown in the remaining 13 cases. Lacrimal sac specimens were submitted for routine histopathologic examination and the direct-smear fluorescent antibody test. All specimens were negative for chlamydia. Possible reasons for the low detection rate of chlamydia in the trachomatous group were the frequent finding of clinically inactive disease, common canalicular obstruction, and loss of the epithelial lining in the lacrimal sac.

TRACHOMA, a disease caused by *Chlamydia trachomatis*, presumably causes tear flow obstruction from the repeated infection of the mucosal surfaces of the canaliculi, lacrimal sac, and nasolacrimal duct.[1] In countries of the Middle East, North Africa, and Southeast Asia, trachoma is a common cause of lacrimal passage obstruction. Approximately 60% of patients with severe inactive trachoma have either distal nasolacrimal duct or canalicular obstruction.[2]

Since previous studies on conjunctival specimens from patients with clinically inactive trachoma have detected the chlamydial organism, the possibility of active chlamydial disease in the lacrimal sac exists. If active disease were present in the lacrimal sac, then postoperative dacryocystorhinostomy patients may be at an increased risk for surgical failures because of scarring at the surgical anastomotic site. Postoperative treatment with antitrachomatous antibiotics may then be indicated in this select group of patients to lessen the likelihood of surgical failure.

To investigate the possibility of active chlamydial disease in the lacrimal sac, we submitted lacrimal sac specimens for routine histopathologic examination and the direct-smear fluorescent antibody test from patients undergoing dacryocystorhinostomies in a region endemic for trachoma.

Material and Methods

We studied 35 consecutive patients undergoing dacryocystorhinostomies in whom the causes of their nasolacrimal duct obstructions were either presumed trachoma or unknown. All of the patients were seen and treated at the King Khaled Eye Hospital between January 1985 and June 1986. All patients were examined for the presence of tarsal conjunctival scarring, corneal pannus, or Herbert's pits. All patients with trachoma had inactive disease as evidenced by at least two of the above findings.

A dacryocystorhinostomy with excision of the posterior lacrimal sac as a specimen was performed in all cases. Blunt and sharp dissection of any obstructing membranes causing common canalicular obstruction was performed to allow passage of silicone tubes from the superior and inferior canalicular system. Suturing of the anterior lacrimal sac and anterior nasal mucosal flaps was then performed. The lacrimal sac specimen was bisected and one half was submitted for routine histopathologic examination and the other half was smeared onto a glass slide for direct immunofluorescent staining. This test contained fluorescein isothiocyanate-labeled monoclonal antibodies specific for the principal membrane proteins of *C. trachomatis*. These antibodies detect all 15 known serologic types of the organism.

After the lacrimal sac epithelial surface was

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From the Department of Ophthalmology, University of Arkansas for Medical Sciences, Little Rock (Dr. Rice) and the Department of Ophthalmology, University of Cincinnati Medical School, Cincinnati (Dr. Kersten). This study was performed in Saudi Arabia and was supported by the Research Department, King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia.

Reprint requests to Charles D. Rice, M.D., Department of Ophthalmology, University of Arkansas for Medical Sciences, Mail Slot 523, W. Markham, Little Rock, AR 72205.

smeared onto the preformed well of the glass slide, the slide was air dried, fixed with acetone, and stored at −20 C. Specimens were stained from one to two weeks after preparation. The lyophilized fluorescent-labeled antiserum was reconstituted with distilled water and allowed to remain at room temperature for 30 minutes. Thirty microliters of the reagent was added to each smear. The slides were then incubated in a moist chamber for 15 minutes. The reagent was aspirated and the slides rinsed in distilled water for 10 seconds. The slides were removed and allowed to air dry. Examination was performed with a fluorescent microscope under ×400 magnification for screening and ×1,000 magnification for confirmation of the structures found. These were reviewed in a masked fashion by laboratory staff trained in this field and by one of us (C.D.R.). The size of the particles, their structure, and the degree of immunofluorescence were used as criteria for regarding specimens as positive. Specimens were considered positive if five or more elementary bodies were seen on a smear. Both positive and negative controls were included in each series.

The surgery was considered successful if 2% fluorescein dye was detected nasally after instillation into the conjunctival cul-de-sac or irrigation of saline fluid demonstrated patency into the nose. If irrigation showed blockage, the surgery was considered a failure, regardless of the patient's symptoms. Results of surgery in the 35 patients were evaluated in two categories (Table) based on the presence of clinical trachoma and the site of nasolacrimal duct obstruction. There were 30 patients available for follow-up in each category. Follow-up intervals were recorded for the period from surgery to silicone tube removal and also the period from silicone tube removal to the last follow-up examination.

TABLE
SURGICAL RESULTS

CAUSE	NO. OF CASES	NO. LOST TO FOLLOW-UP	SUCCESS RATE NO. SUCCESSFUL/ TOTAL	(%)
Trachoma	22	5	13/17	(76)
Nontrachoma	13	0	12/13	(92)
Common canalicular obstruction	15	3	8/12	(67)
Distal nasolacrimal duct obstruction	20	2	17/18	(94)

Results

Of the 35 patients, 22 (63%) had evidence of inactive trachoma and 13 (37%) had no clinical signs of trachoma. There were 16 men and 19 women who ranged in age from 21 to 80 years. Patients with inactive trachoma ranged in age from 34 to 80 years (mean, 47 years). Patients without clinical evidence of trachoma ranged in age from 21 to 57 years (mean, 45 years). There was no significant difference in sex distribution between the two groups.

Surgery was successful in 13 of 17 patients (76%) with trachoma who were followed up compared to 12 of 13 patients (92%) without clinical trachoma who were followed up (Table). Of 12 patients with common canalicular obstruction who were followed up, surgery was successful in eight (67%) as compared to 17 of 18 patients (94%) with distal nasolacrimal duct obstruction who were followed up.

Common canalicular obstruction was present in 12 of 22 patients (55%) with trachoma and three of 13 patients (23%) without trachoma.

The interval from surgery to silicone tube removal ranged from one to 12 months (average, six months in the trachomatous group and nine months in the distal nasolacrimal duct obstruction group). The last follow-up examination after silicone tube removal averaged six months in each group.

Histopathologic findings—We examined the epithelial surface, lymphocytic infiltration, and lymphoid follicles of the lacrimal sac. The lacrimal sac epithelial surface was thinned or absent in 16 of 22 (73%) trachomatous cases and five of 13 (38%) nontrachomatous cases. All of the specimens showed lymphocytic infiltration and several from each group had plasma cell infiltrates in significant numbers. No follicles were seen in the specimens.

Immunofluorescent findings—Two patients were found to have chlamydial organisms. A 50-year-old man and a 54-year-old woman with inactive trachoma were found to have one and two elementary bodies, respectively. Both had distal nasolacrimal duct obstructions with a patent common canalicular system.

Discussion

Trachoma results in obstruction of the tear flow from the presumed chlamydial infection of the mucosal surfaces of the canaliculi, lacrimal

sac, and nasolacrimal duct.[1] Trachomatous patients with nasolacrimal duct obstruction typically have inactive trachoma.[2,3] The potential for such patients having active chlamydial disease in the lacrimal sac exists since chlamydiae have been detected in conjunctival specimens of patients with inactive trachoma.[4] If active disease were present in the lacrimal sac of trachomatous patients undergoing dacryocystorhinostomies, then postoperative treatment with antitrachomatous antibiotics may be indicated to lessen the likelihood of surgical failure. The potential for this complication was significant in our series since 22 of 35 (63%) of our patients had inactive trachoma.

The direct-smear fluorescent antibody technique was selected as the method for detecting chlamydiae in our series because it is a rapid, efficient, and inexpensive technique.[5-9] The sensitivity and specificity of this test in both clinical and experimental conditions compares favorably with the tissue culture method.[6,7] In our series, none of the specimens were considered positive, since the identification of at least five elementary bodies was required for positivity. Two patients in the trachomatous group had one and two elementary bodies, respectively. No elementary bodies were detected in the 13 patients without clinical trachoma. Patients without clinical trachoma were included in this series since it was not known if chlamydial disease could be present in the lacrimal sac of patients with possible subclinical infection.

Previous studies attempting to isolate chlamydia from the lacrimal sac have been performed with the the egg yolk inoculation technique and Giemsa stain.[10,11] Vali, Goswani, and Gupta,[10] using the egg yolk inoculation technique, failed to demonstrate the trachoma agent in nine lacrimal sac specimens from patients with inactive trachoma. Mitsui[11] demonstrated inclusion bodies within the lacrimal sac in one of 13 patients with chronic inactive trachoma.

Because 15 of our patients had common canalicular obstruction, the decision to perform either a standard dacryocystorhinostomy or a conjunctivodacryocystorhinostomy with insertion of a Jones tube was considered. Since a dacryocystorhinostomy was performed in all of our cases, consideration of the possible chlamydial infection of the lacrimal sac was important. If a conjunctivodacryocystorhinostomy would have been performed, then the question of active chlamydial disease in the lacrimal sac would be clinically unimportant since the Jones tube would bypass any active infection.

We carefully examined the degree of obstruction in patients with common canalicular obstruction. In all cases, complete obstruction and not stenosis was found. This was confirmed by the presence of the "wrinkle sign" when attempting to pass a No. 0 Bowman probe through the common canalicular area.[12] Failure to irrigate distally was used as confirmation of the complete blockage at the common canalicular site.

Common canalicular obstruction has generally been managed with a conjunctivodacryocystorhinostomy and an indwelling bypass tube. However, there is significant patient and physician dissatisfaction with this procedure.[13-15] Hurwitz and Rutherford[16] reported a 77% success rate in patients with common canalicular obstruction in whom dilation or blunt and sharp dissection of obstructing membranes was performed in combination with placement of temporary silicone tubes. We have been similarly impressed that a conjunctivodacryocystorhinostomy can often be avoided by this approach. Even though our success rate in patients with common canalicular obstruction was 67%, the avoidance of repeated visits and possible multiple procedures required of patients with Jones' tubes seemingly justify a dacryocystorhinostomy as the initial procedure. If a dacryocystorhinostomy is not successful, then a Jones tube can be placed through the dacryocystorhinostomy anastomosis.

By current methods, detectable chlamydial infection in the lacrimal sac is not common in patients with inactive trachoma. In the trachomatous group, possible explanations for this finding are the presence of clinically inactive disease and the frequent finding of both common canalicular obstruction and loss of the epithelial lining in the lacrimal sac. Therefore, in most cases, treatment in the postoperative period with antitrachomatous antibiotics is not needed.

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OPHTHALMIC MINIATURE

Floating upward through a confusion of dreams and memory, curving like a trout through the rings of previous risings, I surface. My eyes open. I am awake.

Cataract sufferers must see like this when the bandages are removed after the operation: every detail as sharp as if seen for the first time, yet familiar too, known from before the time of blindness, the remembered and the seen coalescing as in a stereoscope.

Wallace Stegner, *Crossing to Safety*
New York, Random House, 1987, p. 3

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EDITORIAL

On Lectureships in Ophthalmology

Frank W. Newell

In 1950 Arnold Knapp wrote a JOURNAL editorial with the above title (Am. J. Ophthalmol. 33:134, 1950). He listed ten lectures that he stated made serious demands on suitable speakers and on appropriate titles. He suggested that rather than being given annually, the lectures should be given only when the circumstances warrant. To honor the name of an outstanding ophthalmologist he suggested a money stipend and not a medal. Additionally, Knapp suggested that the prize be bestowed for the report of original laboratory or clinical investigations.

A recent review of named lectures and awards in American ophthalmology suggested that the number of lectures has increased enormously during recent years. The following list is by no means complete; nonetheless its length suggests that Knapp's admonition has gone unheeded.

Corrections, additions, and deletions to the list are welcome.

Lecture/Award	Sponsor
Francis Heed Adler	University of Pennsylvania
Mary K. Asbury	University of Cincinnati
Taylor Asbury	Cincinnati Society of Ophthalmology
Walter S. Atkinson	International Eye Foundation Society of Eye Surgeons
Francisco J. Bajandas	University of Texas, San Antonio
Arthur J. Bedell	Wills Eye Hospital

(Continued)

William L. Benedict	Ophthalmic Publishing Company/Minnesota Academy of Ophthalmology
Conrad Berens	Contact Lens Association of Ophthalmologists
Alson E. Braley	University of Iowa
Ferdinand Phinizy Calhoun, Jr.	Emory University
Ramon Castroviejo	Castroviejo Society
Paul A. Chandler	Harvard University
Paul A. Chandler–W. Morton Grant	New England Ophthalmological Society
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Claude L. Cowan	National Medical Association
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Edward J. Curran	University of Kansas
George E. de Schweinitz	College of Physicians of Philadelphia
John H. Dunnington	National Society to Prevent Blindness
Edwin B. Dunphy	Massachusetts Eye and Ear Infirmary
F. Bruce Fralick	University of Michigan
Jonas S. Friedenwald	Association for Research in Vision and Ophthalmology
Sanford R. Gifford	Chicago Ophthalmological Society
Everett L. Goar	Houston Ophthalmological Society
Harry S. Gradle	Pan-American Association of Ophthalmology
DuPont Guerry III	The Medical College of Virginia
John E. Harris	University of Minnesota
Edward Lorenzo Holmes*	Institute of Medicine of Chicago
Howe Lectureship	Howe Foundation (Boston)
Howe Medal	American Ophthalmological Society
Prize Medal (Howe)	Section on Ophthalmology, American Medical Association
Howe Medal	University of Buffalo
Lucien Howe Award	Medical Society of the State of New York
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Alex E. Krill	University of Chicago
Peter C. Kronfeld	University of Illinois
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Ralph I. Lloyd	Brooklyn Ophthalmological Society
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Murray F. McCaslin	Eye and Ear Hospital of Pittsburgh
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LETTERS TO THE JOURNAL

Pseudomonas Corneal Ulcer Associated With Colored Cosmetic Contact Lenses in an Emmetropic Individual

Karla J. Johns, M.D., and Denis M. O'Day, M.D.

Department of Ophthalmology, Vanderbilt University School of Medicine. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc. (D.M.O.).

Inquiries to Karla J. Johns, M.D., D-5217, Vanderbilt Medical Center North, Nashville, TN 37232.

A 14-year-old girl had a three-day history of pain, decreased vision, and discharge in the right eye. She was emmetropic and occasionally wore daily-wear colored soft contact lenses to make her blue eyes appear green. The lenses had been worn two days before the onset of symptoms. There was no history of antecedent ocular disease or trauma.

A densely infiltrated 4-mm ulcer was present in the paracentral cornea and was associated with a small hypopyon. Visual acuity was R.E.: counting fingers at 8 feet and L.E.: 20/20. *Pseudomonas aeruginosa* was isolated on corneal culture. The infection responded well to intensive treatment with topical gentamicin (13.6 mg/ml) and cephazolin (50 mg/ml). After one month of treatment, the patient's visual acuity in the right eye was still reduced to 20/40 because of a residual corneal scar.

When the patient was questioned about her contact lens care, she said she cleaned and disinfected them after each use with a one-step hydrogen peroxide system. The lenses were worn intermittently and were stored in a contact lens case with unpreserved saline for days or weeks at a time. Culture of the contact lens and residual fluid yielded a heavy growth of mixed gram-positive and gram-negative bacteria.

The risk-benefit ratio must be considered for each patient before contact lenses are prescribed. There are many potential benefits to the ametropic individual, which usually outweigh the small but real risk of potentially blinding complications, most notably corneal infections. Emmetropic patients who wear colored soft contact lenses risk serious ocular sequelae for the sake of cosmesis alone. Additionally, patients who wear these lenses intermittently may perceive their lenses to be merely a cosmetic aid and, therefore, may be more prone to unsafe practices than daily wearers accustomed to a regular pattern of contact lens hygiene. The widespread advertising of colored cosmetic contact lenses in fashion magazines creates a demand among emmetropic patients while failing to mention the associated risks. Ophthalmologists may see more contact lens-related corneal ulcers in such individuals as these cosmetic colored soft contact lenses gain popularity.

THE JOURNAL welcomes letters that describe unusual clinical or pathologic findings, experimental results, and new instruments or techniques. The title and the names of all authors appear in the Table of Contents and are retrievable through the Index Medicus and other standard indexing services. Letters must not duplicate data previously published or submitted for publication. Each letter must be accompanied by a signed disclosure statement and copyright transfer agreement published in each issue of THE JOURNAL.

Letters must be typewritten, double-spaced, on 8 1/2 x 11-inch bond paper with 1 1/2-inch margins on all four sides. (See Instructions to Authors.) They should not exceed 500 words of text. A maximum of two black-and-white figures may be used; they should be cropped to a width of 3 inches (one column). Color figures cannot be used. References should be limited to five.

Letters may be referred to outside editorial referees for evaluation or may be reviewed by members of the Editorial Board. All letters are published promptly after acceptance. Authors do not receive galley proofs but if the editorial changes are extensive, the corrected typescript is submitted to them for approval.

These instructions markedly limit the opportunity for an extended discussion or review. Therefore, THE JOURNAL does not publish correspondence concerning previously published letters.

Systemic Factors Affecting Diabetic Macular Edema

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A 48-year-old man with a 16-year history of diabetes mellitus and a two-year history of hypertension was initially seen in September 1985. The patient had received panretinal photocoagulation in both eyes and had undergone a vitrectomy in the right eye at another institution in 1981. On examination, his best corrected visual acuity was R.E.: 20/400 and L.E.: 20/25 (J1). Mild lenticular changes were observed in both eyes. Results of ophthalmoscopic examination disclosed a foveal hole in the right eye. In the left eye, mild residual fibrovascular tissue was noted along the superotemporal arcade; however, no macular edema was seen on biomicroscopic examination.

On Jan. 14, 1986, the best corrected visual acuity in the left eye had decreased to 20/40 (J3). Clinically observed cystoid macular edema was confirmed by fluorescein angiography (Fig. 1). The patient had a previously placed arteriovenous fistula in anticipation of hemodialysis because of progressing renal failure. Because of the onset of macular edema, his nephrologist agreed to initiate hemodialysis on Jan. 17, 1986. His predialysis weight was 113.6 kg and his blood pressure was 200/116 mm Hg. On Feb. 20, 1986, his best corrected visual acuity had improved to 20/25 (J1), his weight had decreased to 106.8 kg, and his blood pressure had decreased to 160/70 mm Hg. Biomicroscopy showed that the cystoid macular edema had resolved clinically with only mild residual leakage angiographically (Fig. 2).

In May 1986, the patient underwent a successful cadaveric renal transplant. On his last follow-up visit in January 1987, visual acuity in his left eye remained 20/25 (J1), with no clinical evidence of macular edema. His weight remained approximately 106 kg and he discontinued the nadolol, methyldopa, and furosemide, which had been required to control his hypertension and fluid retention before hemodialysis.

Previous investigators have demonstrated a decrease in diabetic macular edema after renal transplantation[1] and after peritoneal dialysis or medical control of hypertension with diure-

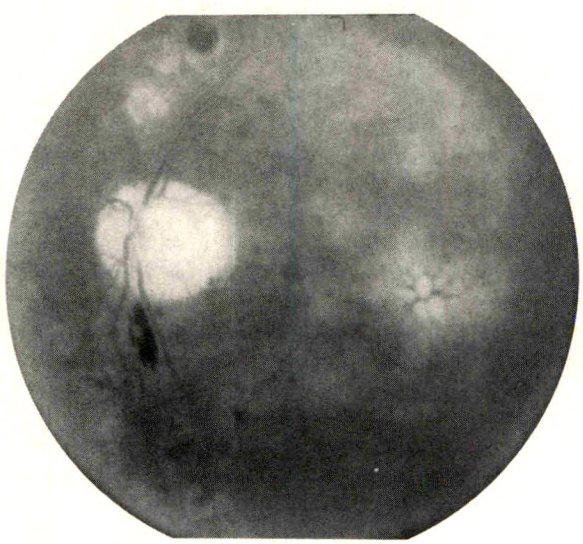


Fig. 1 (Perkovich and Meyers). Late phase fluorescein angiogram showing severe cystoid foveal edema.

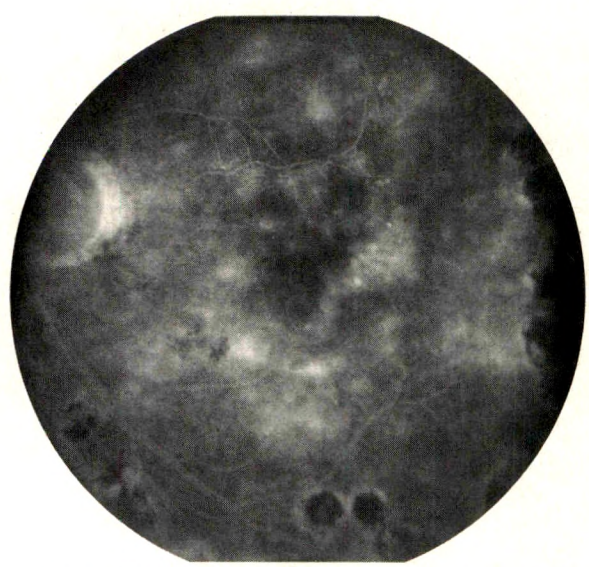


Fig. 2 (Perkovich and Meyers). Follow-up angiogram showing only mild residual perifoveal leakage.

sis.[2,3] Furthermore, hypertension has been associated with diabetic macular edema in epidemiologic studies.[4]

This case is unique because it demonstrates a relatively rapid decrease of diffuse diabetic cystoid macular edema of recent onset after hemodialysis, and a sustained effect after renal transplantation. It emphasizes the importance of systemic factors such as increased blood pressure and fluid overload in diabetic macular edema, particularly in the diffuse form. Although we have seen two similar cases, the overall frequency with which these systemic factors play a clinically significant role is unknown, as is the time frame in which the cystic changes and edema are reversible. Prompt aggressive control of systemic hypertension and fluid overload may potentially obviate the need for perifoveal laser treatment and, therefore, should be considered in patients with diabetic macular edema.

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Ischemic Optic Neuropathy in Sickle Cell Disease

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Symptomatic vascular occlusions of the retina[1,2] (central, branch, and macular arteriole occlusion) and choroid[3] have been associated with sickle cell diseases, including sickle cell anemia, sickle cell trait, sickle cell thalassemia, and sickle cell hemoglobin C disease. We describe a patient with sickle cell hemoglobin C disease who developed bilateral ischemic optic neuropathy and unilateral retinal infarction.

A 21-year-old black woman with hemoglobin SC disease developed severe visual loss in both eyes during the fourth week of pregnancy. Her medical history was significant for several sickle crises manifested by pain in the joints. Results of neuro-ophthalmic examination one month later disclosed visual acuities of R.E.: 20/20 and L.E.: 10/400. Results of Goldmann perimetry showed a small inferior temporal island of vision remaining on the left, and marked superior depression of all isopters on the right. A large afferent pupil defect was noted in the left eye. Results of slit-lamp examination were unremarkable. Normal conjunctival vessels were observed. Ophthalmoscopy (Figure) and fluorescein angiography showed pallid optic disk edema on each side, and narrowed retinal arterioles. There was occlusion of the left macular branch arteriole and opacification of the wall of the inferotemporal arteriole. Although several areas of left peripheral vascular occlusion at the equator were noted, there were no evident sea fans. Results of laboratory tests, including hematocrit, serum viscosity level, coagulation profile, computed tomography, and lumbar puncture, were normal. There was no improvement in visual acuity on follow-up examination one year later.

Abnormalities of the optic nerve with sickle cell disease are unusual. In 1978, Goldbaum, Jampol, and Goldberg[4] described segmentation of blood within small disk vessels in nine asymptomatic patients with sickle cell hemoglobinopathies. It was believed that transient, non-visually significant occlusive phenomena occurred on the disk surface, perhaps likened to what may be occasionally seen in the conjunctival circulation. Although rare, neovascularization of the optic disk may occur in association with severe diffuse retinal ischemia. Posterior ciliary artery occlusion with choroidal infarction has been previously described and documented histopathologically.[5] The extensive collateral circulation of the optic nerve (circle of Zinn Haller) may prevent ischemic optic neuropathy in young patients with sickle disease. Although hormonal alterations or other changes related to pregnancy might

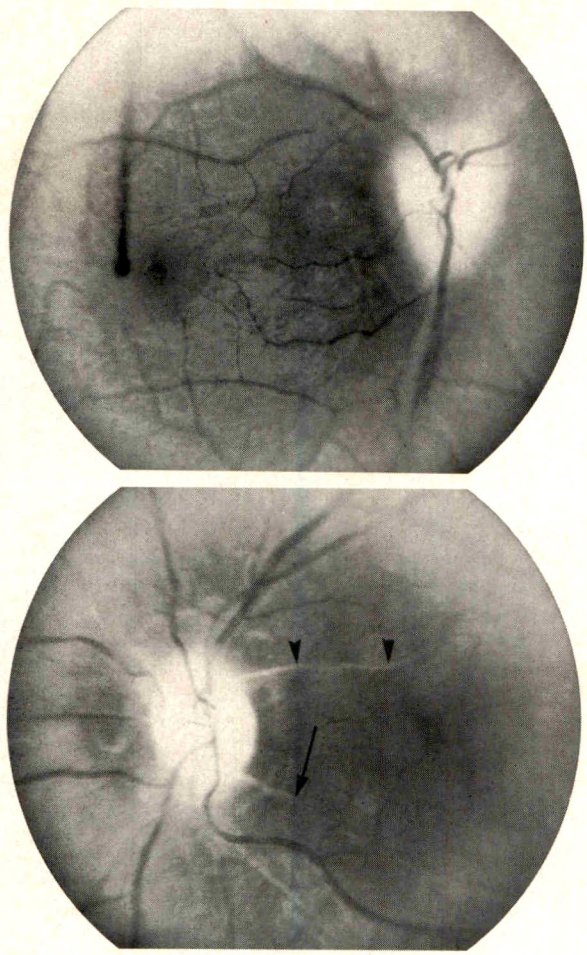


Figure (Slavin and Barondes). Top, Bilateral disk edema and optic atrophy, one month after the onset of visual loss. Bottom, left macular branch artery occlusion (arrowheads), and opacification of the wall of the inferotemporal arteriole (arrow).

lower the threshold for sickling to occur, our patient manifested no other sickle crises during the course of an otherwise uncomplicated pregnancy.

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Immunosuppressive Acidic Protein in Behcet's Disease

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Isolated from cancerous ascitic fluids, immunosuppressive acidic protein is a type of α-1-acid glycoprotein. Its behavior in immunoelectrophoresis and immunodiffusion is indistinguishable from that of normal human α-1-acid glycoprotein. However, this protein differs from normal α-1-acid glycoprotein in its gel isoelectric focusing, its molecular weight, and its carbohydrate content. This protein is produced by human peripheral monocytes, peripheral granulocytes, and the liver. In monocytes, the production of this protein is stimulated by the presence of immune complex IgG-anti-IgG.

In vitro, the protein suppresses both phytohemagglutinin-induced lymphocyte blast formation and mixed-lymphocyte reaction. Because increased levels are often found in patients with cancer, immunosuppressive acidic protein has been used as a marker for diagnosing malignancies. In patients with inflammatory diseases such as lupus erythematosus, increased levels of this protein have been reported.[1,2] Behçet's disease is a systemic inflammatory disease in which ocular inflammatory signs often occur before other systemic manifestations. In such cases, it is difficult to diagnose.

We investigated the serum level of immuno-

suppressive acidic protein in 32 patients with both Behçet's disease and ocular manifestations, in 60 patients with other types of uveitis, and in 50 normal subjects.

Single radial immunodiffusion assay was used to quantitate levels of the protein in sera. Agarose gel containing anti-immunosuppressive acidic protein goat serum was prepared on a glass plate, and wells 2.5 mm in diameter were punched out. Placed in each well was 5 μl of sample. After incubation for 48 hours at 37 C, the diameter of the precipitation ring was measured.

The mean ± S.D. of the serum immunosuppressive acidic protein level in cases of Behçet's disease was 596.9 ± 133.2 μg/ml, which was significantly greater than that of other uveitis patients (376.5 ± 134.7 μg/ml; $P < .001$) and normal subjects (381.4 ± 62.3 μg/ml; $P < .001$).

The serum immunosuppressive acidic protein level in cases of Behçet's disease in a state of remission (521.5 ± 63.9 μg/ml) was less than that of patients with an active disease state ($P < .01$), but significantly higher than that in normal subjects ($P < .001$) (Figure).

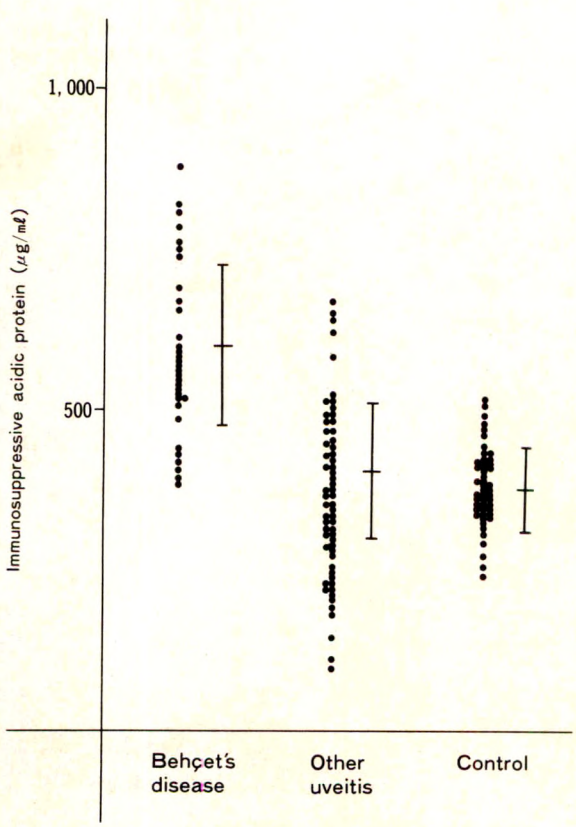


Figure (Yamaguchi and associates). Serum immunosuppressive acidic protein levels in patients with Behçet's disease, other types of uveitis, and in normal controls.

Shimakawa and Kogure[3] reported that serum acid-soluble protein is a useful indicator of activity in Behçet's disease. In our study, the changes of immunosuppressive acidic protein levels were quantitatively correlated with the serum levels of α-1-acid glycoprotein. However, the level of protein showed a relatively higher response. This indicates that immunosuppressive acidic protein levels may be used as a marker for Behçet's disease.

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Hyaluronate in the Identification of the Cut End in Lacerations of the Lacrimal Canaliculi

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Repair of a lacerated lacrimal canaliculus requires exquisite microsurgery to obtain postoperative patency. Ideally, surgery should be performed within 24 hours after trauma. Visual identification of the medial cut end of the lacerated canaliculus is often difficult, even through the operating microscope. Current

methods of facilitating recognition of this cut end include injection of milk or of a white ophthalmic suspension through a blunt cannula via the intact canaliculus, as well as injection of air under a pool of saline.[1] Colorants such as methylene blue should not be used, as they stain the surrounding tissues, rendering recognition of the cut end more difficult.

To recognize the medial cut end of the canaliculus, we have been using a mixture of hyaluronate with fluorescein. To prepare the mixture, an ampulla of hyaluronate (0.4 ml) is emptied in a medicine glass, and two drops of 2% fluorescein solution are added. Stirring is followed by aspiration of the mixture in a syringe. The stained hyaluronate is then injected through the intact canaliculus. Injection causes filling of the lacrimal sac and reflux through the injured canaliculus.

Viscoelastic properties of the hyaluronate and slow injection allow a controlled reflux. Thus, only a fraction of a drop is allowed to protrude through the medial cut end of the canaliculus. This end is thus easily recognized, while fluorescein tissue staining is avoided. A cobalt blue filter may be used to enhance visualization.

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A Simple Extrusion Needle With Flexible Cannula Tip for Vitreoretinal Microsurgery

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In eyes with a complex retinal detachment requiring pars plana vitrectomy, internal drainage of subretinal fluid may be performed by various techniques.[1] Drainage may be accomplished by a posterior intentional retinotomy with subsequent drainage of subretinal fluid by an extrusion needle.[2] When an open peripheral break is present, a flexible cannula up to 18 mm can be introduced into the break to allow drainage of posterior subretinal fluid.[3]

The standard 20-gauge extrusion needle can be modified simply by attaching a short flexible cannula to the tapered metal tip (Fig. 1). The silicone cannula tubing* can be attached to the end of the tapered extrusion needle without adhesives. This flexible, 24-gauge tubing can be cut in variable lengths, depending on the expected extension into the subretinal space. The flexible cannula can be folded over to facilitate entry into a 20-gauge pars plana sclerotomy site (Fig. 2).

The flexible cannula can be introduced into an existing peripheral or posterior iatrogenic retinal break and guided into the subretinal space. During simultaneous fluid/gas exchange,[4] the subretinal fluid will passively leave the eye through the extrusion needle cannula. If a peripheral retinal break is used, complete removal of posterior subretinal fluid may not be possible, but reattachment of the peripheral retinal break can be achieved. This would allow laser endophotocoagulation treatment around the retinal break.

In addition to internal drainage of subretinal fluid, the extrusion needle with flexible cannula tip has many applications in vitreoretinal microsurgery. In association with the vacuum cleaning/extrusion technique, the soft, flexible

*The silicone cannula tubing is manufactured by Dow Corning (HH075305).

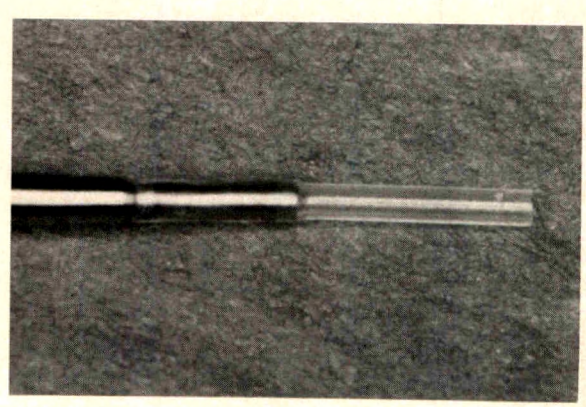


Fig. 1 (Flynn, Lee, and Parel). A flexible cannula is attached to the end of a tapered 20-gauge extrusion needle.

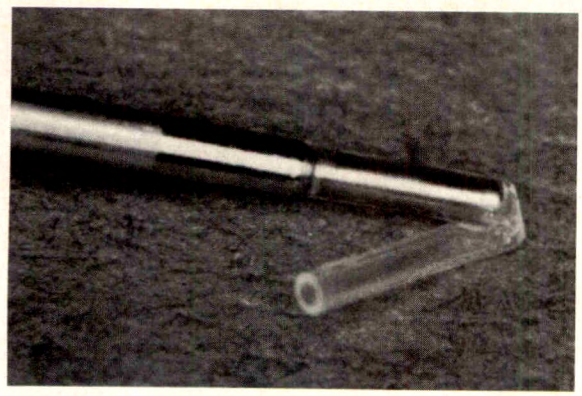


Fig. 2 (Flynn, Lee, and Parel). The flexible cannula can be folded over to allow entry into a 20-gauge pars plana sclerotomy site. The cannula will return to its straight position when it enters the vitreous cavity.

tubing is useful for the removal of preretinal hemorrhage in patients with diabetes. It is useful in reaching subretinal gas bubbles or subretinal blood adjacent to an open retinal break. Finally, to achieve a better position of the retinal flap in selected cases of giant retinal tear, this instrument can be used to push anteriorly the edge of the tear during simultaneous fluid/gas exchange.

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Full-Frame Angiography for the Zeiss Fundus Camera

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The standard 30-degree Zeiss fundus camera produces an excellent, but slightly oval, fundus photograph. It is approximately 25 mm in diameter and is marred only by the four surrounding dark corners devoid of information. This oval central image, although excellent in quality, has the obvious disadvantage of using less than 90% of the area available in the typical 35-mm frame. To overcome this minor flaw, I devised a simple extension tube to enlarge the image size of the Zeiss FF3 fundus camera. The image retains all the horizontal information of the standard frame, but maintains the superior optics of the camera system, including excellent capillary detail.

To produce 1.5× image magnification, a 13-mm extension tube was fitted with a high minus lens that was ground to fit the interior of the tube. The 13-mm extension tube length and

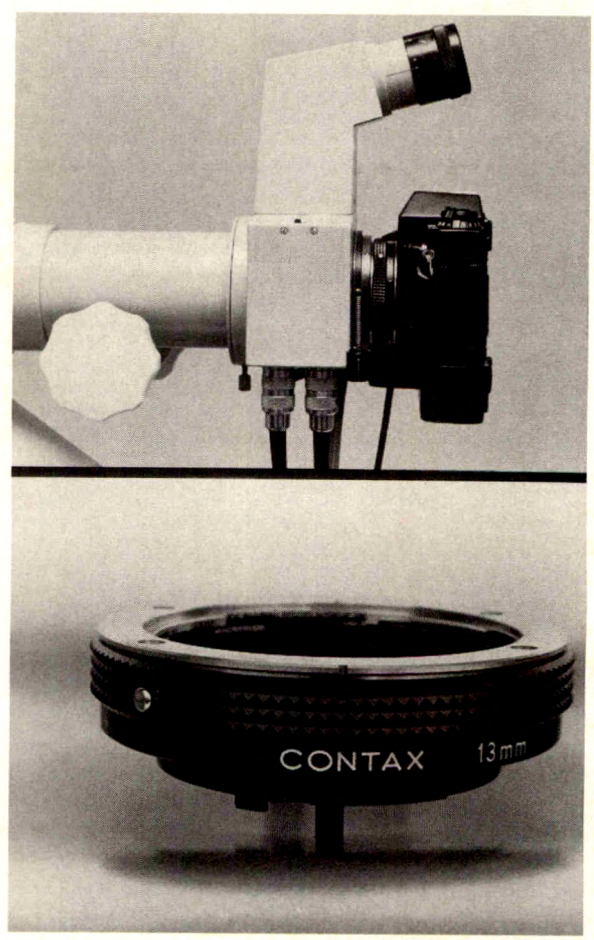


Fig. 1 (Campo). Top, Extender unit mounted on the camera back, between the mounting ring and the eyepiece head. Bottom, 1.5× extender tube with internal minus lens.

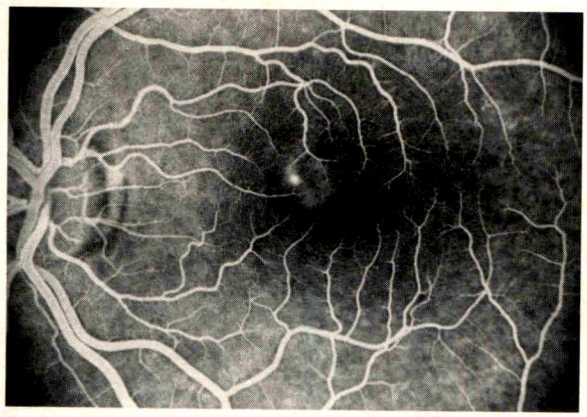


Fig. 2 (Campo). Modified full-frame angiogram produced by 1.5× extender. Horizontally, all information from the original 25-mm oval is retained and expanded, although a small amount of the image along the vertical meridian is sacrificed.

the −11.0-diopter internal lens were found to be the proper combination to form a sharp image that fills 98% of the available area of the frame. Contax extension tubes mated with the Contax RTSII camera backs used in our office. If different camera backs are used, then matching extension tubes will be needed. The extension tube mounts between the camera body and mounting ring (Fig. 1). Zeiss makes a 1.6× extender similar to the more familiar Zeiss 2× extender, both of which attach to the outside of the mounting ring and in front of the eyepiece head. When the barrier filter is in place, however, these units fail to fit flush with the camera body. This prevents their use during fluorescein angiography.

Our 1.5× extender is used primarily for fluorescein angiography (Fig. 2), although it can also be used for color fundus photography. Exposure compensations must be made. For color photographs, the exposure is increased from 60 W seconds to 120 W seconds. Red-free photographs are exposed the same as without the extender, with the lowest power settings available. This is true for both our Dyonics power supply, as well as our SBG720 power unit. Angiography is done by increasing the power to two times the original setting used for standard 30-degree angiography. I have used this system for the past three years without harm to the camera. The detail, clarity, and esthetics of the angiograms have been especially gratifying.

Use of Specular Photomicrography With a New Type of Film

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Recent advances in specular microscopy, such as optical improvements for greater width of field and use of computerized video-scanning for quantitative image analysis, have led to better evaluation of the corneal endothelium.[1] In the past, we photographed the endothelial cell mosaic using Kodak Tri-X Pan film. Despite its grainy appearance, this film allows assessment of both cell density and structure while permitting concurrent development with fluorescein angiograms. Recently we used a new film, Kodak T-Max 100, which greatly enhanced both image contrast and resolution for improved specular photomicrography documentation.

Kodak T-Max 100 film utilizes tabular grain technology,[2] which consists of silver halide crystals that have a stippled, thin, wafer-like configuration. This configuration increases the light-gathering potential and permits extremely fine grain and high spatial resolution in the negative. This offers greater sensitivity compared to the cubic silver halide crystal configuration used in Tri-X Pan film.

Combined with finer grain structure, this new technology creates an emulsion with more efficient conversion of incoming photons to a higher resolution image without sacrificing film speed. Although T-Max 100 is rated at ISO/ASA 100, its grain structure is finer than the less sensitive Panatomic-X (ISO 32). When compared with Tri-X, the greater resolving power is readily apparent (Figure). In high-contrast regions, such as at cell borders, T-Max 100 resolves 200 lines per millimeter, compared with 100 lines per millimeter with Tri-X (100% increase in spatial resolution). In low-contrast areas, such as intracellular detail, a resolving power of 63 lines per millimeter exists compared to 50 lines per millimeter for Tri-X (26% increase in spatial resolution).

We use T-Max 100 film in a Keeler-Konan Pocklington Specular Microscope with a 30× objective lens, a green contrast filter, and with

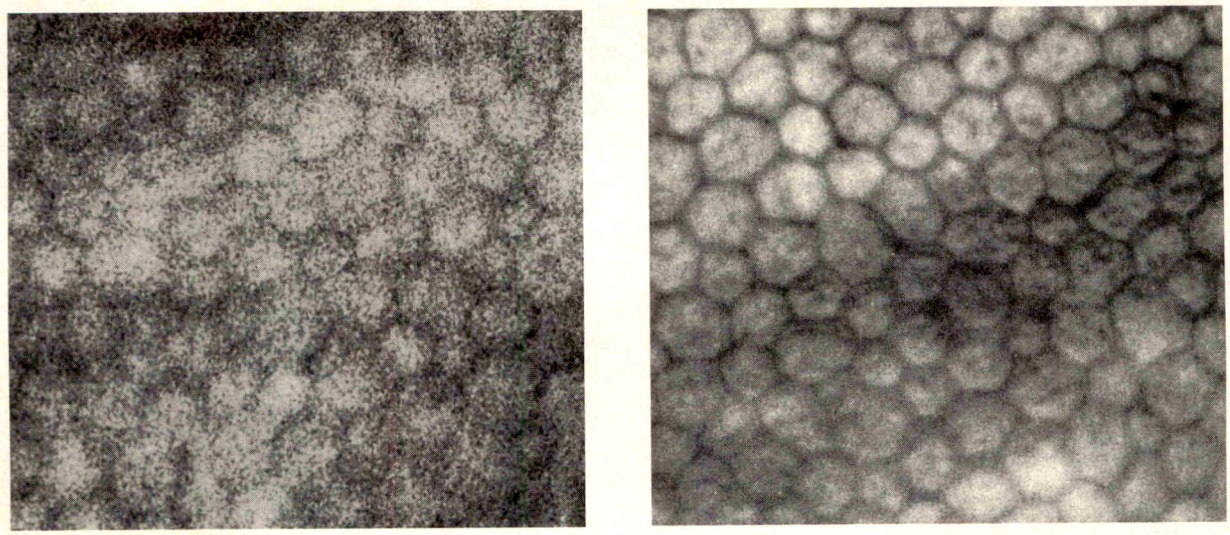


Figure (Carlson and associates). Left, Mild pleomorphism and polymegethism, photographed using Kodak Tri-X Pan film with a Pocklington Specular Microscope. Right, The same eye, photographed using Kodak T-Max 100 film. Improved spatial resolution permits visualization of greater cellular detail (×400).

the flash power selector set on the "high" position. Since we process both T-Max 100 film and fluorescein angiograms using Kodak HC-110 developer (dilution A) for five minutes at 22 C, they can be processed simultaneously. In addition to being convenient, this produces excellent results for improved documentation by specular photomicrography.

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Correspondence

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Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

An Analysis of the Effect of Intravitreal Blood on Visual Acuity

EDITOR:

In the article, "An analysis of the effect of intravitreal blood on visual acuity," by J. T. Thompson and K. M. Stoessel (Am. J. Ophthalmol. 104:353, October 1987), the authors correctly point out that small amounts of vitreous blood can substantially decrease visual acuities. However, the experimental model described was ambiguous and may be misleading.

The luminance of the screen used was not noted. The standard recommended luminance is 85 candelas per meter squared. Because recognizability of high-contrast images is directly affected by the brightness of the surrounding area, acuity measurements obtained using a bright screen may be better than those obtained using a standardized screen.

The authors simulated a light-scattering environment by turning on incandescent overhead lights. This degraded the contrast of the test image on the screen and increased the light scatter in the blood chamber. The authors' conclusion that "the visual acuities of 20/20 measured with room lights at the lower concentrations of blood were qualitatively worse . . . because of light scatter" is uncertain. Decreased contrast of the optotypes alone, particularly if it was less than 30%, could cause a decrease in visual acuity.

Because of light scatter, the perception of high-contrast images is a relatively poor indicator of visual disability. Patients with good high-contrast acuity may still have significant impairment of visual function. Thus, the authors' statement that "1.04 μl of blood caused no reduction in visual acuity . . . " could be misleading.

Opacities in the ocular media posterior to the lens cause more discrete shadows on the retina than similar defects anterior to the lens. If the test chamber is positioned in front of the eye, then the effect of visual clouding on visual acuity may be misleading.

Another limitation on the validity of this study is that only two subjects were included, and each made repetitive observations on the same chart. The chart, itself, consists of a limited number of large letters. This method is prone to unintentional memorization.

Although this study helps "explain certain clinical observations about vitreous hemorrhage," the methods used may not demonstrate accurately the severity of visual function degradation associated with vitreous hemorrhage.

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Reply

EDITOR:

Our study was based on a model of the effect of intravitreal blood on visual acuity. It has all of the limitations of any model that analyzes a complex biologic process. Dr. Lempert criticizes the use of a standard high-contrast visual acuity chart. The visual acuities were measured with a Snellen chart projected onto a metallic silver-gray screen. This visual acuity system is used by many, if not a majority of ophthalmologists who test visual acuities in patients with diffuse vitreous hemorrhage. Dr. Lempert does not cite any published evidence to prove the superiority of a different type of visual acuity chart in the determination of visual acuity in eyes with diffuse vitreous hemorrhage.

The decreased visual acuities measured at some concentrations of hemorrhage with overhead lights may be caused by a number of factors. Light scattering appears to be the most important factor. Dr. Lempert's assertion that decreased acuity from light scatter is different than decreased acuity from decreased contrast is incorrect. One of the effects of light scatter is to decrease the contrast between the dark letters and white background on the Snellen chart.[1]

We agree that the perception of high-contrast images may not be the best measure of visual disability. The purpose of our study, however, was to measure visual acuity in a model of diffuse vitreous hemorrhage, not to assess visual disability. We also stated that this model of visual acuity was only applicable to diffuse vitreous hemorrhage. Dr. Lempert expresses concern about unintentional memorization of the acuity chart causing bias in the results. This was controlled by testing the various concentrations of hemorrhage in a random double-masked fashion in each subject. The close agreement between the two subjects and the strong correlation of increased hemorrhage density with decreased visual acuity suggest that the testing procedure did not bias the results.

Much additional research on the effect of diffuse or focal media opacities on visual acuity remains to be done. We hope that our article helps stimulate additional studies on the effect of vitreous hemorrhage on visual acuity.

JOHN T. THOMPSON, M.D.
KATHLEEN M. STOESSEL, M.D.
New Haven, Connecticut

Reference

1. Miller, D. A.: Physical optics. In Duane, T. D., and Jaeger, E. A. (eds.): Clinical Ophthalmology. Philadelphia, Harper and Row, 1986, pp. 5–10.

Limbal- vs Fornix-Based Conjunctival Trabeculectomy Flaps

EDITOR:

In the article, "Limbal- vs fornix-based conjunctival trabeculectomy flaps," by C. E. Traverso, K. F. Tomey, and S. Antonios (Am. J. Ophthalmol. 104:28, July 1987), the authors compared limbal-based and fornix-based conjunctival trabeculectomy flaps. Their study confirms the equal efficacy of the two methods in terms of safety and short-term efficacy of pressure control. It should, however, be

remembered that a number of such eyes later require cataract operation, and it is here that the fornix-based flaps have their disadvantage. The fornix-based flaps result in more anteriorly positioned blebs. Even though in most cases the blebs appear identical in two groups in the fullness of time, to an extent the limits of a fornix-based flap extend significantly to cover the clear corneoscleral limbus. This means that during cataract surgery, via a corneal section, either one has to interfere with the drainage bleb or approach the cataract through an unusually anteriorly placed corneal section. For this reason at least, the limbal-based conjunctival flap should be the preferred method for trabeculectomy.

NIKHIL C. KAUSHIK, F.R.C.S.
Wrexham, United Kingdom

Reply

EDITOR:

The comments of Dr. Kaushik are well taken. Although during the follow-up period of our study we could not show any difference in bleb configuration between the two groups, a more anterior extension of the bleb in the fornix-based conjunctival flaps is a possibility. We have greatly decreased surgical difficulties of lens extraction after filtering surgery by adopting extracapsular cataract extraction from the temporal approach, with or without intraocular lens implantation. This, in our hands, has avoided the problems related to bleb manipulation or corneal sections in either limbal- or fornix-based conjunctival flaps.

CARLO E. TRAVERSO, M.D.
KARIM F. TOMEY, M.D.
SOBHI ANTONIOS, M.D.
Riyadh, Saudi Arabia

Histopathologic and Immunohistopathologic Features of Subretinal Fibrosis and Uveitis Syndrome

EDITOR:

In the article, "Histopathologic and immunohistopathologic features of subretinal fibrosis and uveitis syndrome," by M. K. Kim, C.-C. Chan, R. Belfort, Jr., M. Farah, M. P. Burnier, R. B. Nussenblatt, T. Kuwabara, and A. G. Palestine (Am. J. Ophthalmol. 104:15, July 1987), the authors conclude that the subretinal fibrosis and uveitis syndrome "appears to be clinically and histopathologically distinct from other forms of intraocular inflammation." In 1949 Fuchs[1] reached approximately the same conclusion in his description of a new fundus disease, which he called choroiditis proliferans.

According to Fuchs, choroiditis proliferans is a rare disease in which large areas of connective tissue form on the inner side of the choroid. Although the retina shows only slight changes, there is a marked loss of vision in both eyes.

Fuchs described a 16-year-old Albanian with congenital syphilis who had particularly bad vision in each eye for 3 years.[1] Visual acuity in the left eye was counting fingers at 5 m. Visual field testing showed considerable constriction for hand movements temporally, above, and below. A Wassermann reaction was positive. The patient had first received antisyphilitic treatment three years earlier. Ophthalmoscopic findings were similar in each eye.

> The disk is somewhat pale. The retinal vessels are somewhat narrow. Atrophy of the choroid is scarcely visible anywhere. Peculiar ragged, sharply defined, dead-white tissue bundles extend over the entire posterior pole. They pass around the disk, ramify, and finally break up like flames. The retinal vessels pass over them in a straight course. The sinewy glistening appearance indicates connective-tissue membranes. Far to the right and partly on the left side, old pigmented choroiditis patches may be observed. The pigment epithelium is rarefied and nasal to the disk as a result of pigment migration. It is questionable whether the connective-tissue bundles originate from the choroid or from the retinal disease. The former appears more probable. It is certain that the connective-tissue lies between the pigment epithelium and the retina. The inner retinal layers hardly seem to have been affected. The external ones, however, have been involved considerably. This may be recognized by the poor vision.

In comparing Fuchs' description of choroiditis proliferans to the authors' description of subretinal fibrosis and uveitis syndrome, it occurred to me that the subretinal fibrosis and uveitis syndrome and choroiditis proliferans may be the same disease.

I would like to know the authors' opinion about the similarities.

NASSIM CALIXTO, M.D.
Belo Horizonte, Brazil

Reference

1. Fuchs, A.: Diseases of the Fundus Oculi With Atlas. Philadelphia, The Blakiston Company, 1949, pp. 125–127.

Reply

EDITOR:

Fuchs described an exceedingly rare bilateral condition characterized by marked subretinal gliosis and an irreversible decrease in visual acuity. It would certainly seem that this disorder is the same as the one that we reported in our article. A caveat would be that Fuchs did not have the opportunity to observe the clinical course in this patient. Further, it would be necessary to exclude the other disorders that may mimic the subretinal fibrosis and uveitis syndrome. It is rewarding to read that Fuchs believed this to be a unique entity as well. We are indebted to Dr. Calixto for bringing this to our attention.

MYUNG K. KIM, M.D.
São Paulo, Brazil
CHI-C. CHAN, M.D.
Bethesda, Maryland
RUBENS BELFORT, JR., M.D.
MICHEL FARAH, M.D.
MIGUEL P. BURNIER, M.D.
São Paulo, Brazil
ROBERT B. NUSSENBLATT, M.D.
TOICHIRO KUWABARA, M.D.
ALAN G. PALESTINE, M.D.
Bethesda, Maryland

Visual Recovery in Combined Central Retinal Artery and Central Retinal Vein Occlusion

EDITOR:

The article "Visual recovery in combined central retinal artery and central retinal vein occlusion," by P. A. Jorizzo, M. L. Klein, W. T. Shults, and M. L. Linn (Am. J. Ophthalmol. 104:358, October 1987), reminded me of a similar publication by Cassen, Tomsak, and DeLuise,[1] which was not cited.

In this paper, we also described two patients with this condition. One suffered from classic migraine and the other had several prodromal episodes of transient monocular blindness. Both were otherwise healthy. We documented improvement in intraretinal circulation in the man, aged 32 years, by serial-timed, intravenous fluorescein angiograms over a period of 30 days. The woman, aged 38 years, did not improve and subsequently developed neovascular glaucoma. We speculated that this condition might represent a severe variant of papillophlebitis.

ROBERT L. TOMSAK, M.D.
Cleveland, Ohio

Reference

1. Cassen, J. H., Tomsak, R. L., and DeLuise, V. P.: Mixed arteriovenous occlusive disease of the fundus. J. Clin. Neuro-ophthalmol. 5:164, 1985.

Reply

EDITOR:

We thank Dr. Tomsak for calling our attention to his two patients, each of whom had fundus findings similar to those we described. We regret our oversight in not citing his study.

PAUL A. JORIZZO, M.D.
MICHAEL L. KLEIN, M.D.
WILLIAM T. SHULTS, M.D.
MERRITT L. LINN, M.D.
Portland, Oregon

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Presbyopia. Recent Research and Reviews From the Third International Symposium. Edited by Lawrence Stark and Gerard Obrecht. New York, Professional Press Books, 1987. 510 pages, index, illustrated. $95

Reviewed by BENJAMIN MILDER
St. Louis, Missouri

This collection of papers presented at the Third International Symposium on Presbyopia is, without question, the most comprehensive work ever assembled on this topic. It offers an overview of the entire field, with 66 papers presented by and for a multidisciplinary group that included ophthalmologists, optometrists, optical scientists, psychologists, and manufacturers.

There are eight sections. The first covers "the human dimension": epidemiology, ethnology, and environmental factors. The second section deals with the biochemical and physical properties of the crystalline lens and lens capsule.

The third group of papers comes to grips with the sensory mechanisms of presbyopia, particularly the alterations in the visuosensory processes that accompany aging as well as those induced by corrective lenses.

All corrective lenses produce some distortion. The fourth section explores the subject of adaptation by the presbyopic individual to these distortions. Since the progressive lens wearer has voluntarily elected a form of presbyopic correction that distorts the surrounding world, he or she will adapt to the lenses despite persisting sensory awareness. One excellent study, by Levy-Schoen and associates, disclosed that reading performance is not affected by moderate image defocusing (less than 2 diopters); beyond that, although saccades and visibility span are unchanged, reading speed is significantly reduced.

The fifth section is devoted to the accommodation-convergence-pupil constriction triad and, in many ways, retraces well-worn paths, including the apparent paradox of the absence of asthenopic symptoms despite increased near exophoria in the presbyopic patient. It is suggested that fixation disparity measurements provide a more realistic appraisal of the near fusion status than the usual clinical phoria-vergence testing.

The ten papers in the sixth section consider the specific requirements of the individual in the correction of presbyopia.

Woo found that determination of the proper add power was not influenced by the configuration of clinical test charts or by illumination (between 3.5 and 220 foot-candles), but that sine and square wave gratings yielded much higher accommodation values than the test charts.

The seventh group of papers concerns the means of correcting presbyopia, with emphasis on progressive lenses and contact lenses. Borish's well-constructed study found that early presbyopic individuals, particularly those with no prior lens experience, overwhelmingly preferred progressive lenses to bifocals. Older presbyopic individuals who wear trifocals were evenly split on the desirability of a shift to progressives. Meltzer's work on the use of progressives for pseudophakic individuals pointed up the importance of accurate, skilled dispensing of progressives.

There were discussions of the various options in the use of contact lenses for presbyopia. Of particular interest was a preliminary investigative report by Vestal and Miller demonstrating reversible changes in refracting power of soft contact lenses by immersing the lens in various concentrations of urea. Equally fascinating was Kern's work in which he passed a current across thin film molecular optical materials to alter the refraction of an optical system.

The two-column format is admirably suited to this large volume. Most chart and figures have been reduced to the point that legends are not readable. There is an enormous bibliography covering the last 75 years. While this book could hardly be called bedside reading, it provides a broad overview of the field, investigative as well as clinical, biologic as well as sociopsychological. There is something for everyone.

The Retina. An Approachable Part of the Brain. By John E. Dowling. Littleton, Harvard University Press, 1987. 282 pages, index, illustrated. $37.50

Reviewed by DONALD G. PURO
Miami, Florida

Over the past 25 years, scientists have made remarkable progress toward understanding how the retina functions. Many who are not neurobiologists are aware that these are exciting times in retinal research, but the voluminous literature and evolution of technical jargon are formidable hurdles to those interested in getting an overview of progress in this field. Fortunately, John Dowling has addressed the need for a readable overview of what is known about the functional organization of the vertebrate retina. He has written a book that conveys with clarity the excitement of advances in retinal research.

Dowling, who has made major contributions to retinal research, emphasizes the great progress achieved by the use of a multidisciplinary approach involving anatomy, biochemistry, physiology, and pharmacology. Key experimental observations in retinal research are described clearly and supplemented with helpful illustrations at virtually every turn of the page. The reader is unlikely to get lost in details since Dowling is willing to speculate on how the experimental findings shed light on the general issue of how the retina is organized. Clinicians with little or no experience in retinal research are likely to find this a readable book. To help those who are not neurobiologists, an appendix serves as a primer for basic concepts and terms in neuroscience. Overall, the book is written at about the level of complexity found in articles in the publication Scientific American.

Early chapters describe the various types of retinal neurons, their synaptic connections, and their characteristic electrical responses. A chapter on retinal pharmacology is a good introduction to an area of investigation that may one day establish a scientific basis for the use of drugs to enhance the function of retinal circuits injured by disease. Although the identification of neurotransmitters and neuromodulators is one of the most rapidly developing areas of retinal research, the information in this text is reasonably up-to-date. Clearly, a disease-oriented approach is beyond the scope of this book. However, the chapters on the basis of the electroretinogram and visual adaptation will provide helpful insights toward understanding clinical electrophysiologic tests of retinal function. References in the book are not meant to be exhaustive, but are sufficient to lead the interested reader into the literature. The index is thorough and should aid in reading selected topics.

The book's subtitle, "An Approachable Part of the Brain," reflects the concept that the retina is an experimentally accessible structure, useful for the study of the neurobiology of the brain. Surprisingly, some neuroscientists need to be reminded that the retina is, indeed, part of the brain. The final chapter illustrates how the study of the retina has contributed toward an understanding of the mechanisms of certain brain functions. As the author notes, the retina may be the best understood part of the central nervous system. This well-written book should be available to all who are interested in how the retina works.

The Vitreous and Vitreoretinal Interface. Edited by Charles L. Schepens and Adolphe Neetens. New York, Springer-Verlag New York, Inc., 1987. 315 pp., index, illustrated. $57

Reviewed by H. RICHARD MCDONALD
San Francisco, California

In this text vitreoretinal specialists and laboratory researchers in ocular disease have successfully combined their knowledge to present the basic science of the vitreous and the role of the vitreous in the pathogenesis of medical and surgical retinal disease. Though each chapter can stand alone as a reference for a particular vitreous-related disease or condition, there is very little overlap of information. The editors are to be commended for constructing a readable, concise, and clear view of the vitreous.

The preface mentions the growing awareness of the physiologic and biochemical importance of the vitreous, speculating on the probable importance of the vitreous in retinal metabo-

lism. The authors strive to point out the role of the vitreous in the healthy eye, as well as the diseased one. Still, the thrust of the book is the way in which vitreous change produces retinal disease. All students of the retina can benefit by understanding the intimate relationship between the vitreous and retina. By doing so, we increase our ability to manage, and perhaps prevent those diseases. For this reason, the book is an important one.

Embryology, biochemistry, anatomy, and normal age-related changes in the vitreous are reviewed. This information is used throughout the rest of the book to explain various vitreoretinal disease states. The tone of the text is decidedly clinical. Topics include the role of the vitreous in rhegmatogenous retinal detachment, traction retinal detachment, aphakia, and retinopathy of prematurity, to name a few.

The sections on the vitreous in ocular trauma, idiopathic giant retinal breaks, hereditary vitreoretinal diseases, and vitreous substitutes are well written and well referenced. Some of the later chapters deal with surgical techniques of vitreous surgery, and provide valuable insights from clinicians with a wealth of experience.

There are in vivo photographs of vitreous changes. As these techniques of objectively recording the vitreous improve, so will our appreciation and understanding of the vitreous in the normal and diseased eye. These vitreous photographs, as well as the color fundus photographs, have lost clarity in reproduction, though the numerous illustrations and schematic drawings are instructive and of good quality.

The section on vitreous changes and macular diseases contains opinions on the role of the vitreous in macular hole and preretinal fibrosis formation, but avoids comment on recent controversies concerning tangential vitreous traction in the production of macular holes or the role of vitrectomy for "impending" macular holes.

This text is informative and valuable for residents and clinicians interested in vitreoretinal disorders. The section on vitreous changes in aphakia and retinal detachment contain ramifications for anterior segment surgeons concerned with minimizing their incidence of postcataract retinal detachment. The authors and editors are to be commended for a well-planned, well-written book.

Contemporary Issues in Ophthalmology—Refractive Keratoplasty. Edited by Ivan R. Schwab. New York, Churchill Livingstone, 1987. 216 pages, index, illustrated. $58

Reviewed by MICHAEL P. VRABEC
and JAY H. KRACHMER
Iowa City, Iowa

Dr. Schwab has assembled an excellent general review of refractive keratoplasty, covering theory, indications, results, and complications. The opening chapter puts the various operations into perspective, and provides an interesting look at the beginnings of refractive surgery.

Werblin, one of the pioneers of epikeratophakia, has written a useful review of the subject. The histopathologic illustrations are splendid. The exact surgical technique has changed since the chapter was written, requiring the reader to look for an update in the current literature. The strengths and weaknesses of the surgery, especially its limitations in keratoconus, pediatric aphakia, and myopia are discussed.

The chapter on keratomileusis gives an unusually clear description of the process. The photographs are excellent and show many devices that the general ophthalmologist does not come in contact with on a daily basis. It is interesting that cryolathing is not the most difficult aspect of the procedure. The chapter on keratophakia by Fogle gives a detailed summary of the optics involved in the surgery as well as a succinct review of the operation and the care of the patient. After a well-written summary of alloplastic corneal lenses, radial keratotomy is discussed. The author believes that radial keratotomy, as it was performed in the United States in 1979, is now obsolete. He gives a nice summary of the postoperative results to date. Later in the book, the complications of corneal refractive surgery are discussed, especially in regard to radial keratotomy. This should give the general ophthalmologist some food for thought before undertaking this surgery.

The chapter on the various keratotomy incisions for astigmatism contains a large amount of data. Unfortunately, there have been few carefully planned studies of this type, which

makes it difficult to draw conclusions from the data. The chapter by Beatty and Schanzlin on the prevention of astigmatism after corneal transplant discusses many practical ways for the surgeon to try to avoid producing the astigmatism in the first place. Wedge resections and relaxing incisions are then discussed. In general, we agree with these authors that a repeat keratoplasty for postoperative corneal astigmatism is a poor choice if the graft is clear. However, when the patient has a very high corneal astigmatism and the surgeon has not performed a great deal of keratorefractive surgery, a repeat transplant might be the best solution. Some good clinical points are made in this chapter about relaxing incisions, such as avoiding relaxing incisions in flat corneas, and avoiding placement of a relaxing incision where there is already an anterior displacement of the wound.

A chapter on laser surgery of the cornea is an excellent review of the development of lasers in corneal work and it puts the various lasers and their potential uses into perspective. The last chapter offers some good advice on how to avoid legal problems when performing refractive keratoplasty.

In summary, this is a fine review of the subject. It is a superb place to begin the study of refractive keratoplasty. We recommend it highly.

An Evaluation of the NIH Research Career Development Award. By Grace M. Carter, John D. Winkler, and Andrea K. Biddle. Santa Monica, The Rand Corporation, 1987. 102 pages, softcover, illustrated. $10

Reviewed by FRANK W. NEWELL
Chicago, Illinois

The Research Career Development Award of the National Institutes of Health is intended to foster the career development and to enhance the research capability of individuals with outstanding potential for contributing to health-related research as independent investigators. Over the last 25 years the NIH has provided 3,800 awards and spent over $400 million on the program.

A review of the program by the Rand Corporation indicates that senior researchers rather than promising researchers who are ready to become independent investigators are given preference. Previous support or postdoctoral fellowships, research grants, or association with a research-intensive institute favors approval. Recipients produced more articles of higher quality (as measured by citation rate), and superior grant applications.

This little book provides a wealth of information for program directors, for award applicants, and for internal review groups.

Books Received

Converting to Phacoemulsification. A Manual for the Surgeon in Transition. By Paul S. Koch. Thorofare, New Jersey, Slack Incorporated, 1987. 69 pages, softcover, illustrated. $19.50

An experienced surgeon reviews his personal approach to cataract surgery and offers advice to the novice. This readable book will be valued by cataract surgeons at all levels of skill.

Colour Atlas of Ophthalmology, ed. 2. By Arthur S. M. Lim and Ian J. Constable. Singapore, P G Publishing Pte Ltd, 1987. 147 pages, index, illustrated. $14

This slim book of high-quality photographs covers many aspects of ophthalmology, and it is addressed to the beginner. This second edition has been improved with some new illustrations and new text.

Night Vision. Current Research and Future Directions. By Working Group on Night Vision, Committee on Vision, Commission on Behavorial

and Social Sciences and Education. 335 pages, softcover, illustrated. $28 (United States, Canada, and Mexico), $33.75 (export)

This report on current research in night vision provides an account of the visual processes involved and it describes available screening procedures for the testing of night vision and the instrumentation used in night-vision research. Included are definitions of twilight, papers on photoreceptor properties, on oculomotor, spatial, and temporal factors in night vision, and on human performance issues. Copies are available from The Committee on Vision, National Research Council, 2101 Constitution Ave. N.W., Washington, D.C. 20418.

Degenerative Retinal Disorders. Clinical and Laboratory Investigations. Edited by Joe G. Hollyfield, Robert E. Anderson, and Matthew M. LaVail. New York, Alan R. Liss, Inc., 1987. 626 pages, index, illustrated. $98

A symposium was held in Sendai, Japan, in September 1986 to honor Professor K. Mizuno on the occasion of his retirement as chairman of the Ophthalmology Department of Tohoku University. Included in this text are the proceedings. Topics covered among the 40 papers in this volume include retinitis pigmentosa and other inherited retinal degenerations in humans and inherited and induced retinal degenerations in laboratory animals.

Clinical Ophthalmology: A Text and Colour Atlas, ed. 2. By James L. Kennerley Bankes. New York, Churchill Livingstone, Inc., 1987. 130 pages, softcover, index, illustrated. $27.50

This is a book for beginners that outlines the rudiments of ophthalmology. The layout is pleasing and the photographs are excellent.

Manual for Eye Examination and Diagnosis, ed. 3. By Mark W. Leitman. Oradell, N.J., Medical Economics Books, 1988. Softcover, 100 pages, illustrated. $18.95

This popular little book is aimed at the medical student who is about to work in an eye clinic. Clear diagrams on every page explain to the student just what it is that an ophthalmologist does, and how he goes about doing it. Two hours spent with this book will take a lot of the mystery out of the first few days in the clinic.

A Dispensing Optician Manual. An Introduction to Vision Care for the New Ophthalmic Technician. By A. J. Zelada. Springfield, Charles C Thomas, 1987. 134 pages, index, illustrated. $28.75

This is a practical guide to the art of dispensing glasses. It is full of valuable tips that range from bending the temples to choosing the right kind of bifocal.

Developments in Ophthalmology. Vol. 15. Cataract Epidemiology. Edited by K. Sasaki, O. Hockwin, and M. C. Leske. Series edited by W. Straub. Basel, S. Karger A.G., 1987. 106 pages, index, illustrated. $58.75.

Sixteen papers presented at the International Cataract Epidemiology Meeting, October 1986, Noto, Japan, under the following headings: (1) Evaluation of Cataract Classification Systems, (2) Issues in Conducting Valid Cataract Prevalence Studies, and (3) Investigations of Cataract Risk Factors.

ABSTRACT DEPARTMENT

Edited by David Shoch, M.D.

Acta Neurologica Scandinavica

Neuro-ophthalmological complications of coronary artery bypass graft surgery. Shaw, P. J., Bates, D., Cartlidge, N. E. F., Heaviside, D., French, J. M., Julian, D. G., and Shaw, D. A. (Dept. Neurol., Royal Victoria Infirm., Newcastle-upon-Tyne, England NE1 4LP). Acta Neurol. Scand. 76:1, 1987.

In a prospective study of neurological complications of coronary bypass surgery, detailed pre- and post-operative bedside ophthalmological evaluation was undertaken in 312 patients. Post-operative neuro-ophthalmologic complications developed in 80/312 (25.6%) patients and included: areas of retinal infarction (17.3%); retinal emboli (2.6%); visual field defects (2.6%); reduction of visual acuity (4.5%); and Horner's syndrome (1.3%). Neuro-ophthalmological complications were not observed in a control group of 50 patients undergoing major peripheral vascular surgery. Ten of 75 patients reviewed at 6 months still had detectable neuro-ophthalmological abnormalities, but functional disability occurred only in those with persistent visual field defects. Multivariant analysis revealed that extra-coronary vascular disease, severe and prolonged duration of heart disease prior to operation, and large drop in haemoglobin level during surgery may predispose to neuro-ophthamological complications. (5 tables, 31 references) —Authors' abstract

Archives of Disease in Childhood

Light transmission of phototherapy eyeshields. Chin, K. C., Moseley, M. J., and Bayliss, S. C. (Children's Unit, St. Peters Hosp., Guildford Rd., Chertsey, Surrey, England). Arch. Dis. Child. 62:970, 1987.

To decrease high levels of ambient light in retinopathy of prematurity or from phototherapy for jaundice, the authors found that practically any eyeshield will reduce light transmission to less than 0.1% the incident light. Commercial eyeshields offer no advantage over handmade ones of cotton, felt, or wool. Layers of woven green fabric were most effective, but even the poorest commercial products were satisfactory. (1 figure, 8 references)—David Shoch

British Journal of Ophthalmology

Some observations on the relation between intraocular pressure reduction and the progression of glaucomatous visual loss. Schulzer, M., Mikelberg, F. S., and Drance, S. M. (Dept. Ophthalmol., Univ. British Columbia, 2550 Willow St., Vancouver, BC, Canada V5Z 3N9). Br. J. Ophthalmol. 71:486, 1987.

The authors developed a quantitative measure of the scotomas in glaucoma, which they term "scotoma mass." This represents the area of scotoma in square millimeters times the depth of the loss in decibels. They applied this measure to the visual fields of 41 patients with chronic open-angle glaucoma. They also studied the intraocular pressure control in these patients and found a highly significant negative correlation. Low mean intraocular pressures tended to correspond to high values of scotoma mass. There was a similar negative correlation if the maximum intraocular pressure reading was recorded only in the preceding time interval. As the disease advances and the visual fields worsen, there may be a natural spontaneous reduction in intraocular pressure. Therefore, there may not be a strong correlation between intraocular pressure and field loss. (2 figures, 8 references)—David Shoch

Efficacy of antiprostaglandin therapy in vernal conjunctivitis. Meyer, E. W. Y., Kraus, E., and Zonis, S. (Dept. Ophthalmol., Rambam Med. Ctr., Haifa 35254, Israel). Br. J. Ophthalmol. 71:497, 1987.

Twenty-seven patients, aged 4 to 18 years, with vernal conjunctivitis who had been treated unsuccessfully with topical corticosteroids and cromolyn sodium were given 0.5 to 1.5 g of aspirin daily, depending on age. The use of all topical medications was discontinued. Of the 27 patients, 24 reported marked improvement.

The palpebral hypertrophy of the upper tarsus did not disappear, but they were smaller and less inflamed. There was marked improvement in punctate keratopathy and in limbal infiltration. Aspirin therapy is not innocuous, but it may be effective in patients who do not respond to topical medications. (1 table, 11 references)—David Shoch

Optic disc drusen and episodic visual loss. Sarkies, N. J. C., and Sanders, M. D. (Dept. Ophthalmol., National Hosp. for Nervous Dis., London, England). Br. J. Ophthalmol. 71:537, 1987.

A 54-year-old woman had repeated episodes of visual loss for 26 years. The loss was transient, but each episode resulted in some loss of visual field, which appeared to be an ischemic optic neuropathy. The patient was treated with corticosteroids, which seemed to help. The authors postulated that the increase in size of the disk drusen interfered with vascular supply to the disks, which resulted in transient ischemic episodes with some residual damage to the disks. Over time her central visual acuity decreased from R.E.: 20/20 to 20/30 and from L.E.: 20/80 to counting fingers. (4 figures, 11 references)—David Shoch

International Ophthalmology

Peripheral proliferative retinopathies. Brown, G. C., Brown, R. H., and Brown, M. M. (910 E. Willow Grove Ave., Wyndmoor, PA 19118). Int. Ophthalmol. 11:41, 1987.

In an etiologic study of 100 consecutive cases of peripheral proliferative retinopathy, about 50% were associated with sickling hemoglobinopathies and 20% with branch retinal vein occlusions. Diabetes caused 10% and another 10% were caused by sarcoidosis, intravenous drug abuse, and occasional other rare diseases. In the remaining 10%, no obvious cause could be found for the development of the neovascularization. (3 figures, 3 tables, 27 references)—David Shoch

Investigative Ophthalmology and Visual Science

In vivo effects of 5-FU on ocular surface epithelium following corneal wounding. Capone, A., Lance, S. E., Friend, J., and Thoft, R. A. (Eye & Ear Inst., 203 Lothrop St., Pittsburgh, PA 15213). Invest. Ophthalmol. Vis. Sci. 28:1661, 1987.

The authors produced epithelial defects in rabbits, injected various doses of 5-fluorouracil, and noted the effect on the healing of the corneal epithelium. A daily dose of 0.05 or of 0.5 mg inhibited mitosis but had no significant effect on the clinical or histologic appearance, or healing rate. When the dose was increased to 5 mg daily, persistent epithelial defects occurred in 22% of the eyes. Thus, the drug is useful in inhibiting mitosis and corneal complications can be minimized or eliminated by using the minimal dose required. (3 figures, 1 table, 33 references)—David Shoch

Journal of Pediatric Ophthalmology and Strabismus

Screening criteria for the detection of retinopathy of prematurity in patients in a neonatal intensive care unit. Brown, D. R., Biglan, A. W., and Stretavsky, M. A. M. (Dept. Pediatr., Magee-Women's Hosp., Forbes Ave. and Halket St., Pittsburgh, PA 15213). J. Pediatr. Ophthalmol. Strabismus 24:212, 1987.

The American Academy of Pediatrics has proposed that all newborns who have had any exposure to added oxygen or a birthweight of less than 2,000 g have an ophthalmologic examination before discharge from the hospital. To evaluate these criteria, the authors examined almost 3,000 such neonates. Fifty-six patients had Grade 3 or 4 retinopathy of prematurity in at least one eye, according to the International Classification of Retinopathy of Prematurity. All 56 infants were exposed to added oxygen for more than 50 days or had a birthweight of less than 1,600 g. The authors suggest that these screening criteria are more realistic than those proposed by the American Academy of Pediatrics and that if these more stringent criteria were adopted, it would eliminate unnecessary ocular examinations and yet identify all significant cases of retinopathy of prematurity. (1 figure, 3 tables, 12 references)—David Shoch

Severe visual loss resulting from occlusion therapy for amblyopia. Simon, J. W., Parks, M. M., and Price, E. C. (Dept. Ophthalmol., Albany Med. Ctr., Albany, NY 12208). J. Pediatr. Ophthalmol. Strabismus 24:244, 1987.

One child with amblyopia who had been patched for 13 days developed a small esotropia in the occluded eye. The patch was then switched to the previously amblyopic eye and the parents noted that the child immediately regressed, was unable to function, and walked into walls. On the fourth day of patching, vision began to improve but alternation was not documented until the 40th day of reverse occlusion. A second child was patched for one month and amblyopia and eccentric fixation were noted when the patch was removed. Patching was discontinued, and three months later full-time occlusion of the originally amblyopic eye was instituted with periodic follow-up for approximately one year. The originally occluded eye was first noted to maintain fixation at age 4 years after nearly two years of reverse occlusion. Full-time occlusion should probably be avoided and children should be monitored in intervals of at least one week per year of age. (13 references)—David Shoch

Journal of the Royal Society of Medicine

Phenylephrine-induced reversible cataract in the mouse. Claoue, C. M. P. (Univ. Bristol, Dept. Ophthalmol., Bristol Eye Hosp., Bristol, England BS1 2LX). J. R. Soc. Med. 80:694, 1987.

Phenylephrine 10% was instilled in three different strains of mice to examine the retinas. In all three strains, lens opacities were produced within 15 minutes and in about 1½ hours the cataracts were milky-white. The lenses began clearing within a period of three to six hours, and by 24 hours all lenses were clear. The authors postulate that these cataracts were produced by transcorneal dehydration of the lens. Instillation of 10% phenylephrine in these mice caused marked retraction of both the upper and lower eyelids, exposing the corneas to drying action and apparently causing some transcorneal dehydration of the lens. By coating the corneas with thick layers of ointment, they were able to prevent the appearance of this reversible cataract. The cataracts all started in the anterior portion of the lens, which seems to support their theory. (1 figure, 6 references) —David Shoch

Neurology

Minimal thyroid ophthalmopathy. Spector, R. H., and Carlisle, J. A. (Neuro-ophthalmol., 980 Johnson Ferry Rd. N.E., Suite 550, Atlanta, GA 30342). Neurology 37:1803, 1987.

In many patients with proptosis, the symptoms are minimal and the patient is euthyroid. The authors have termed this minimal euthyroid Graves' disease. In these patients the authors advise a sequential laboratory approach. First, the levels of thyroxine and triiodothyronine and sometimes a triiodothyronine resin uptake are determined. If these values are normal, then antibody studies (both antimicrosomal and antithyroglobulin) are done. If these results are inconclusive, a study of the thyroid stimulating immunoglobulins may also be performed. Finally, if all tests are negative, a thyrotropin releasing hormone stimulation test can be done. Two other investigations should also be performed: a computed tomographic scan and orbital ultrasonography. The computed tomographic scan should include thin sections and reformated views of the orbit in the axial, coronal, and sagittal planes. Ultrasonography offers quantitative data on the size of the muscles. Using this battery of tests, the euthyroid Graves' syndrome can often be diagnosed. (4 figures, 34 references)—David Shoch

Ophthalmologica

HIV antibody screening of corneal donors. Wilhelmus, K. R., and Farge, E. J. (Dept Ophthalmol., Cullen Eye Inst., Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030). Ophthalmologica 195:57, 1987.

Of 1,517 corneal donors, five (0.3%) were repeatedly reactive for human immunodeficiency virus by enzyme immunoassay. This was about half the rate of seropositivity of blood donors in the same community. Although the rate of positivity was small, it is of great concern since the cornea has been implicated in the transmission of other viral diseases. The authors recommend that all donors have a blood test for the presence of human immunodeficiency virus. If this is not done premortem, then a clot of blood can be obtained from a femoral vessel or the cardiac ventricle postmortem. (2 tables, 12 references) —David Shoch

A new hypothesis on tear film stability. Liotet, S., Van Bijstervesld, O. P., Kogbe, O., and Laroche, L. (Hopital des Quinze-Vingts, 28, rue de Chareanton, F-75012 Paris, France). Ophthalmologica 195:125, 1987.

In order to stabilize tear film on the corneal epithelium, the film thickness must be less than 100 μm and the interface between the tears and the epithelium must have a tension that permits the spreading of the film on the surface. Since the epithelial cells are hydrophobic, the tears must contain a surfactant to allow wetting. It has been postulated that the conjunctival mucus from goblet cells acts as a surfactant, permitting the spread of tears on the ocular surface. The authors, primarily on the basis of electron microscopic studies, believe that this is not the true explanation. In avitaminosis A there may be an increased goblet cell density and yet a keratinized and eroded epithelium. Imprint conjunctival cytologic studies often show normal or increased numbers of goblet cells during a period of intense dryness. Electron microscopy showed numerous vesicles at the superior pole of the epithelial cells, which discharged their filamentous content onto the surface. This content is a particular mucoprotein, which the authors termed glycocalix, that participates in the formation of a cell coat. These glycocalix particles are probably fixed to the cell membrane and microvilli at specific sites. The glycocalix is a mucin with rather low molecular weight and is capable of acting as a surfactant. It appears to be present in all mucosal surfaces that are in contact with biologic fluid. The authors conclude that the disappearance of goblet cells in the sicca syndrome is not the cause of the dryness but the result of it and epithelial cell integrity is essential for tear film stability. Therefore, simply using a tear film substitute for dryness of the eyes is not sufficient; the therapy used should allow for regeneration of epithelial cells. (4 figures, 17 references)—David Shoch

Retina

Bilateral melanocytic uveal tumors associated with systemic non-ocular malignancy. Maro, C. E., Pavan, P. R., Gendelman, D., and Gragoudas, E. (Univ. South Florida, Dept. Ophthalmol., Box 21, 12901 N. 30th St., Tampa, FL 33612). Retina 7:137, 1987.

This patient had bilateral diffuse malignant melanomas of the uveal tract and occult ovarian carcinoma. Histologic examination disclosed that the tumor consisted of a mixture of spindle-shaped cells and epithelioid cells, with malignant cytologic features. Thus, the uveal tumors seen in association with systemic malignancies should be assumed to be malignant. (6 figures, 5 references)—David Shoch

Krypton and argon laser photocoagulation for central serous chorioretinopathy. Novak, M. A., Singerman, L. J., and Rice, T. A. (Retina Associates of Cleveland, 26900 Cedar Rd., Suite 323, Cleveland, OH 44122). Retina 7:162, 1987.

In this retrospective study of 86 eyes with central serous chorio-retinopathy with serous detachment of the macula and fluorescein leakage, three treatment modalities had been used. Forty-five eyes received no treatment, 26 eyes were treated with argon laser, and 15 eyes were treated with a krypton laser. Approximately 20% of the patients who received no treatment had recurrences and about 35% of the argon-treated eyes had recurrences. Conversely, none of the eyes treated with krypton showed recurrence. The difference was statistically significant. The results indicate that the treatment of choice for central serous chorioretinopathy is the krypton red laser. (5 figures, 2 tables, 23 references)—David Shoch

NEWS ITEMS

Send News Items to
Editor
American Journal of Ophthalmology
Suite 1415
435 N. Michigan Avenue
Chicago, IL 60611

The Journal invites information concerning meetings, postgraduate courses, lectures, honors, and appointments. Double space each item and provide the name and address of the responsible author. Announcements of courses, meetings, and lectures must be submitted at least six months before the date of the event.

First Mediterranean Symposium on Behçet's Disease

The First Mediterranean Symposium on Behcet's Disease will be held June 4, 1988, in Istanbul, Turkey. For further information, write Prof. N. Dilsen, Istanbul Faculty of Medicine, Division of Rheumatology, Capa, Topkapi, Istanbul, Turkey.

Eighteenth Mexican Ophthalmological Congress

The Eighteenth Mexican Ophthalmological Congress will be held Sept. 25–29, 1988, in Tampico, Mexico. For further information, write Dr. Celso Ponce Hernandez, M.D., Apartado Postal 972, Tampico, Tamaulipas, Mexico 89000.

Allegheny General Hospital: Advanced Orbital Surgery

Allegheny General Hospital will present a course, Advanced Orbital Surgery: Techniques and Practical Experience, May 13 and 14, 1988, in Pittsburgh, Pennsylvania. For further information, write Continuing Medical Education, Allegheny General Hospital, 320 E. North Ave., Pittsburgh, PA 15212.

Chicago Ophthalmological Society: 40th Annual Clinical Conference

The Chicago Ophthalmological Society will hold its 40th annual clinical conference, May 26–27, 1988, in Chicago, Illinois. For further information, write Julie Hughes, Coordinator, Chicago Ophthalmological Society, 515 N. Dearborn St., Chicago, IL 60610.

Johns Hopkins Hospital: Ophthalmic Nursing Seminar Update '88

The Johns Hopkins Medical Institutions will hold a course, Ophthalmic Nursing Seminar Update '88, April 29, 1988, in Baltimore, Maryland. For further information, write Pamela E. Macedonia, Program Coordinator, Office of Continuing Medical Education, the Johns Hopkins Medical Institutions, Turner 22, 720 Rutland Ave., Baltimore, Maryland 21205.

New York Eye and Ear Infirmary: Sixty-First Annual Clinical Conference

The New York Eye and Ear Infirmary will hold its Sixty-First Annual Clinical Conference, Surgical and Medical Decision Making, 1988, June 3, 1988, in New York, New York. For further information, write Jane Stark, Conference Coordinator, New York Eye and Ear Infirmary, 310 E. 14th St., New York, NY 10003.

Ohio State University: Thirty-First Annual Postgraduate Course in Ophthalmology

The Ohio State University Department of Ophthalmology will present the Thirty-first Annual Postgraduate Course in Ophthalmology: Update in Ophthalmology and Oculoplastic Surgery, March 4–5, 1988, in Columbus, Ohio. For further information, write The Ohio State University, The Center for Continuing Medical Education, 320 W. Tenth Ave., Room A-352, Columbus, OH 43210.

Presbyterian Hospital of Dallas: YAG/Argon Workshop

Presbyterian Hospital will sponsor the Fourth Annual Laser Workshop May 27, 1988, in Dallas, Texas. For further information, write Lela Breckenridge, Presbyterian Hospital of Dallas, Office of Continuing Medical Education, 8200 Walnut Hill Lane, Dallas, TX 75231.

St. Mary's Hospital: Retina Research Fund

The Retina Research Fund of St. Mary's Hospital will sponsor a Retina Symposium, March 18–19, 1988 in San Francisco, California. For further information, write Howard Schatz, M.D., 1 Daniel Burnham Ct., #210, San Francisco, CA 94109.

Stanford University: Basic Science Course in Ophthalmology

The University of California, Davis; Pacific Presbyterian Medical Center; University of California, San Francisco; and Stanford University will hold a Basic Science Course in Ophthalmology, July 5–Aug. 31, 1988, in Stanford, California. Tuition is $1,400. For further information, write J. W. Bettmann, M.D., Depart-

ment of Ophthalmology, A-157, Stanford Medical Center, Stanford, CA 94305.

University of California, San Francisco: Ophthalmology in the Year 2020

The Department of Ophthalmology, University of California, San Francisco will hold a course, Ophthalmology in the Year 2020, June 1–3, 1988, in San Francisco, California. For further information, write Extended Programs in Medical Education, Room 569-U, University of California School of Medicine, San Francisco, CA 94143.

University of Kansas Eye Center: Hands-On Training Course

The University of Kansas Eye Center will present a Hands-On Training Course, April 21–23, 1988, in Kansas City, Kansas. For further information, write Mary Gaston, Kansas Eye Center, 39th and Rainbow Blvd., Kansas City, KS 66103.

University of Michigan: Annual Spring Conference

The Department of Ophthalmology of the University of Michigan will present its annual Spring Conference, May 20 and 21, 1988, in Ann Arbor, Michigan. For further information, write Terry Bergstrom, M.D., Kellogg Eye Center, University of Michigan Medical Center, 1000 Wall St., Ann Arbor, MI 48105.

University of Oklahoma: Neuro-Ophthalmology Course

The University of Oklahoma will present a Neuro-Ophthalmology Conference—Diplopia and the 12th Annual Residents and Alumni Meeting, April 7–9, 1988, in Oklahoma City, Oklahoma. For further information, write University of Oklahoma College of Medicine, Office of Continuing Medical Education, P.O. Box 26901, 3SP511, Oklahoma City, OK 73190.

University of Southern California, Los Angeles: Clinical Problems in Corneal and External Disease

The University of Southern California School of Medicine will present a course, Clinical Problems in Corneal and External Disease, July 30–Aug. 6, 1988, in Los Angeles, California. For further information, write Beverly J. Johnson, Postgraduate Medical Education, University of Southern California, School of Medicine, 1975 Zonal Avenue, Los Angeles, CA 90033.

White Memorial Medical Center: Symposium on Corneal Surgery

The Department of Ophthalmology of White Memorial Medical Center will present a symposium on corneal surgery, March 6, 1988, in Los Angeles, California. For further information, write David J. Fuerst, M.D., Department of Ophthalmology, White Memorial Medical Center, 414 N. Boyle, Los Angeles, CA 90033.

Society of Geriatric Ophthalmology: New Officers

The Society of Geriatric Ophthalmology elected the following officers: President, Frank J. Weinstock; Vice-president, John Norris; Vice-president for programs, Henry Spiro; Secretary-Treasurer, Budd Appleton; and Trustees, Alan Chirls, Ira Eliasoph, Raphael Klapper, and Neil Ross.

Health Information Resources in the Federal Government: Update

Reference Secton, National Library Service for the Blind and Physically Handicapped, Library of Congress, Washington, DC 20542; telephone, (202) 287-9286.

Personals

Thomas M. Aaberg

Effective January 1, Thomas M. Aaberg, formerly a professor of ophthalmology at the Medical College of Wisconsin, became Director of the Emory Eye Center, chairman and F. Phinizy Calhoun, Sr. Professor in the Department of Ophthalmology, and section head of ophthalmology in the Emory Clinic. Dr. Aaberg is Senior Associate Editor of THE AMERICAN JOURNAL OF OPHTHALMOLOGY.

George M. Bohigian

George M. Bohigian was elected chairman of the Council on Scientific Affairs of the American Medical Association.

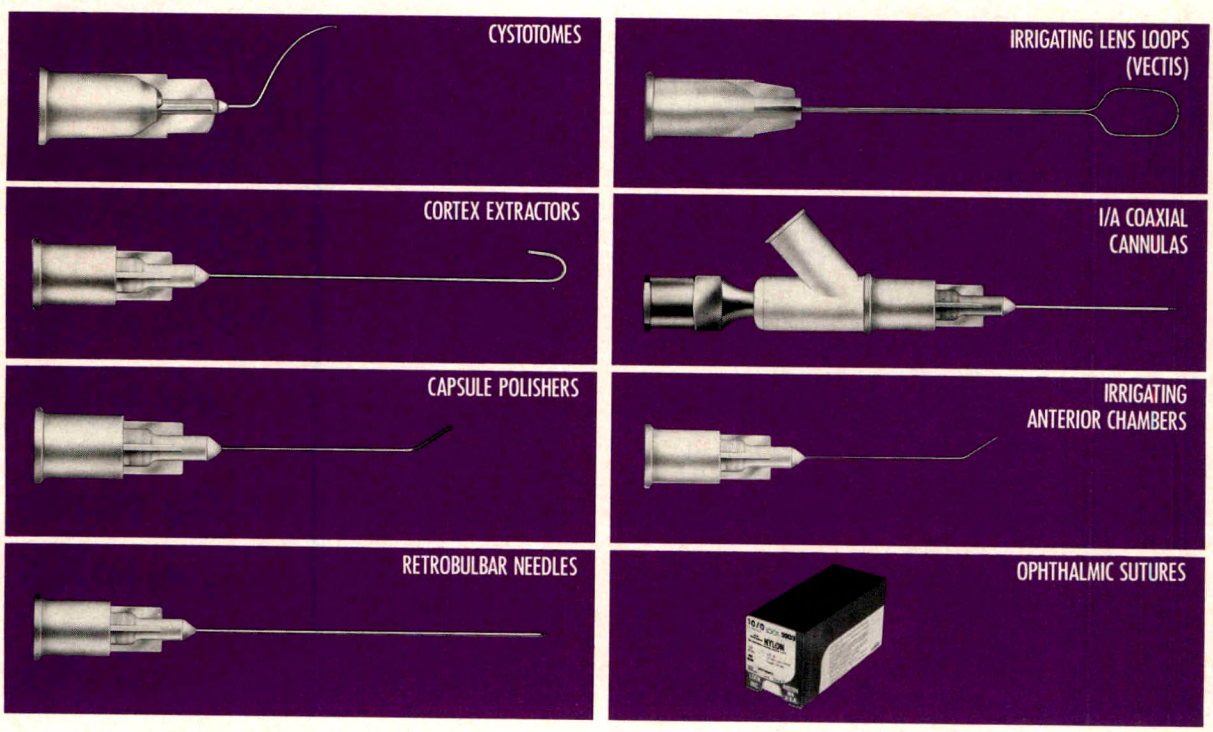
Howard Schatz

Howard Schatz was given the J. E. Brown Memorial Lecture Award in March 1987 at the Ohio State University College of Medicine.

Thom J. Zimmerman

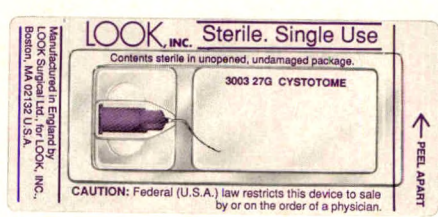
Thom J. Zimmerman received the Heed Award during the 1987 American Academy of Ophthalmology meeting. The award was presented by Frank W. Newell, Chairman of the Board of Directors of the Heed Ophthalmic Foundation.

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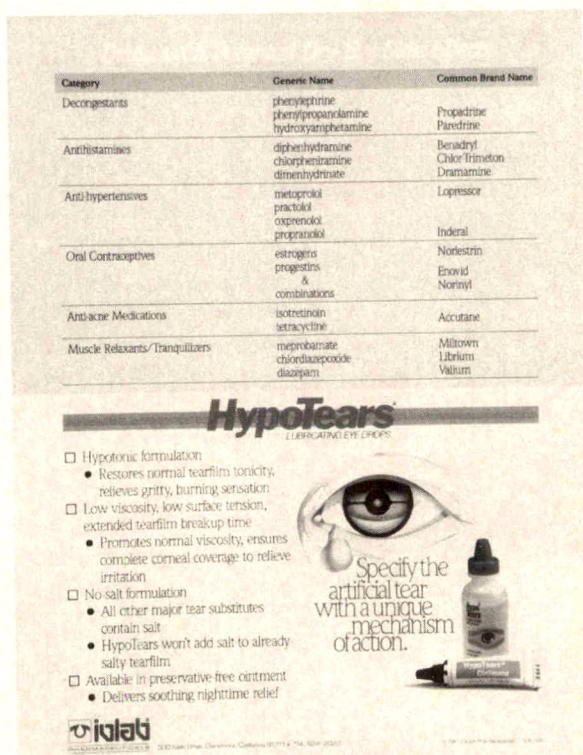
Lowe's Syndrome Association, Inc.
222 Lincoln St.
West Layfayette, IN 47906
Tel: (317) 743-3634

The Lowe's Syndrome Association has published a booklet, "Living With Lowe's Syndrome: A Guide for Families, Friends, and Professionals," which provides medical and developmental information about Lowe's syndrome. It includes genetics, research, and effects on the family. The booklet is free of charge; additional copies are available for $0.50.

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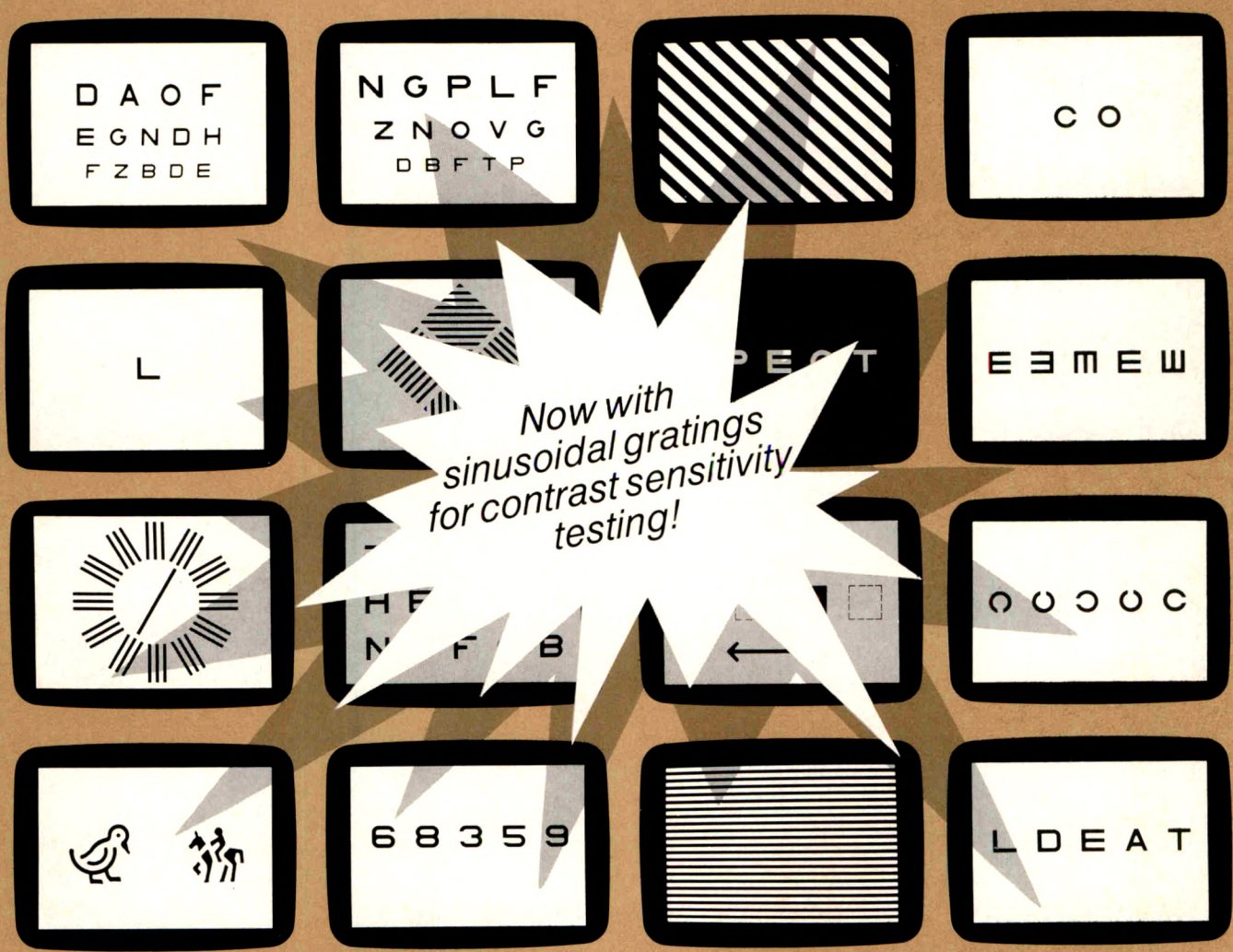
A listing of all publications produced by the Congressional Office of Technology Assessment, including those available in reprints from commercial publishers as well as from the U.S. Government Printing Office and the National Technical Information Service, is now available at no charge. The listing includes order forms and price information.

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IOLAB Pharmaceuticals, a division of Johnson & Johnson, is offering a chart entitled, "Drugs With Potential Dry-Eye Side Effects." This complimentary guide was designed to assist pharmacists in the identification of commonly prescribed drugs that cause dry eye. The pharmacist can advise the patients of this potential side effect and recommend appropriate treatment.

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Vision Sciences, Inc., has announced a major breakthrough for in-office lens casting technology: the capability to cast a solid tint or gradient tint lens as part of its regular lens casting process. The company also announced the ability to cast polarized lenses and they now offer a scratch-resistant coating for use with the Formalens 2000 In-Office Lens Casting System. It is now possible to have the tint permeate evenly throughout the lenses while in the curing oven. Because the tint is below the lens surface there is no possibility of damage to the tint.

Diagnostic Equipment

ICS Medical Corp.
2227 Hammond Dr.
Schaumburg, IL 60173
Tel: (312) 397-2150

ICS Medical Corporation, a manufacturer of eye movement testing instruments for analysis of vestibular pathophysiology, is now making commercial deliveries of its complete rotary test system. The system comprises a chair, which is rotatable about the vertical axis and capable of accelerations in excess of 600-degrees per second per second, an enclosure that provides a light-controlled environment, an infra-red monitoring system, an IBM-AT compatible computer, and the Computerized Tracing System (CTAS) software. The software has been modified to control the rotary stimuli (the rotary chair and optokinetic drum), to store and to analyze the eye movement responses, and to present results in a format that is easily understood and interpreted.

Standard protocol includes sinusoidal acceleration and deceleration at frequencies of 0.01 to 0.64 Hz. The gain, asymmetry, and phase shift of induced eye movement are measured and compared to normal values. Also included is a velocity strip stimulus with which the time constant of the vestibular response can be measured.

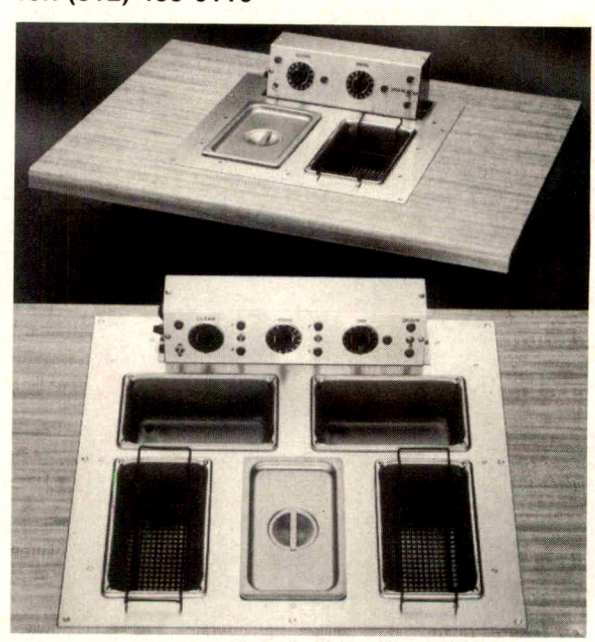
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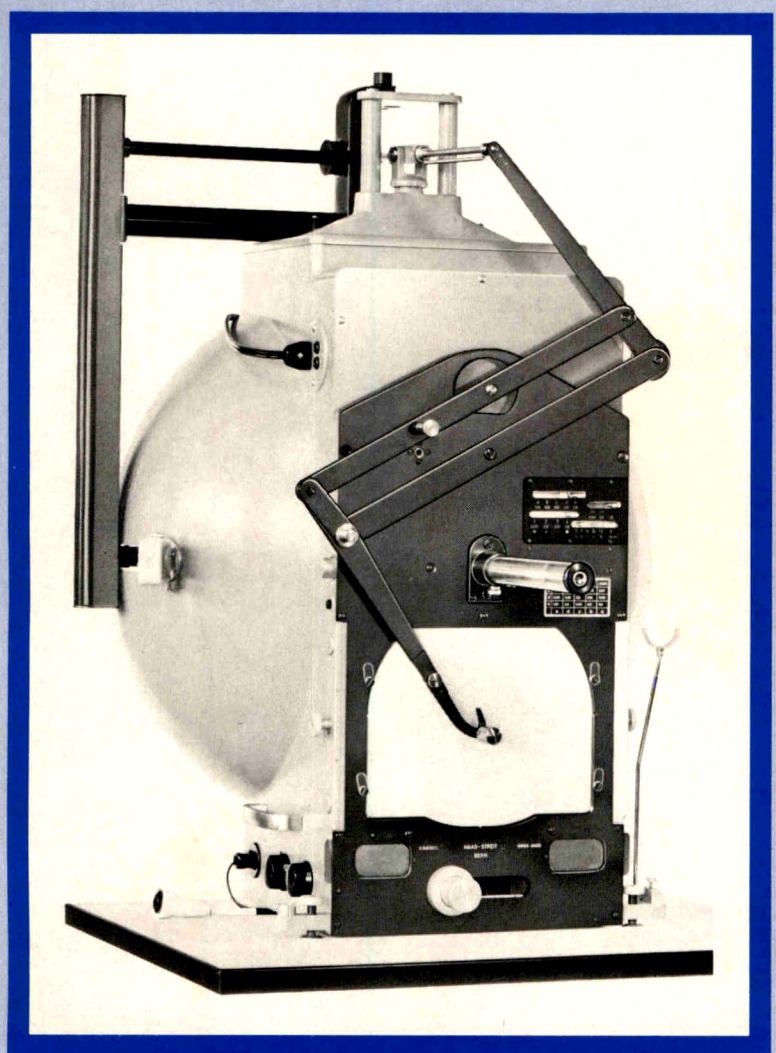
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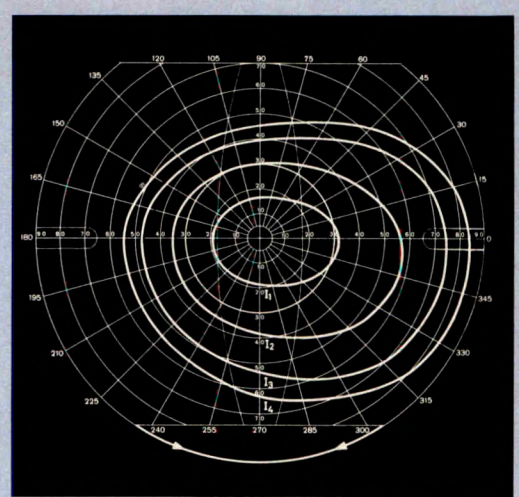


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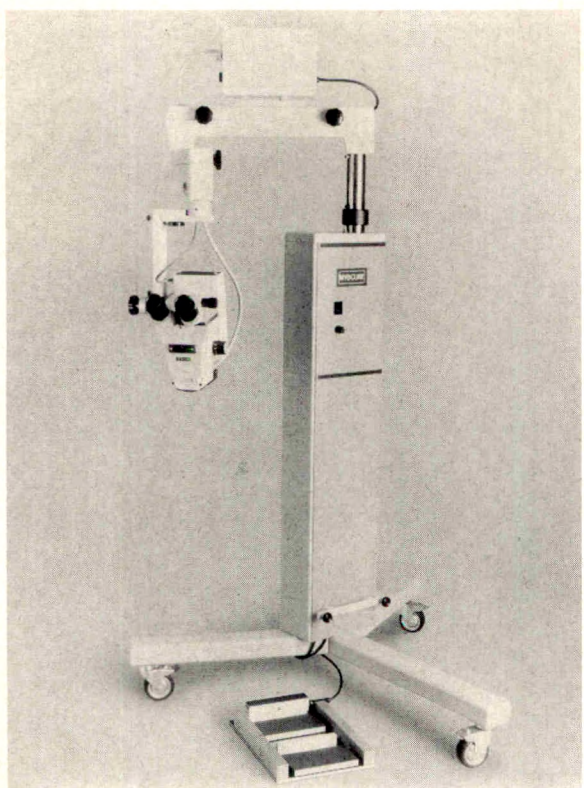
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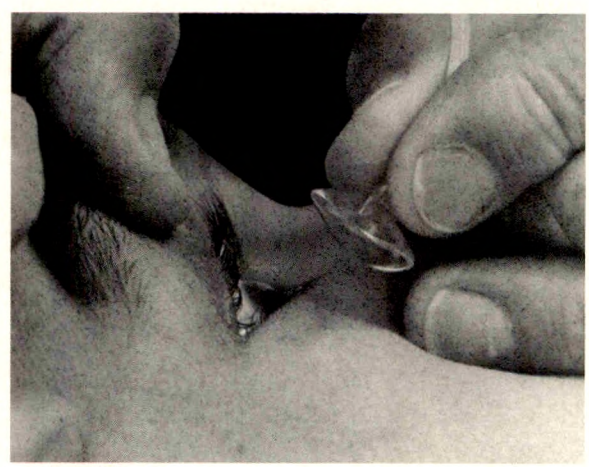
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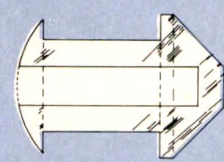
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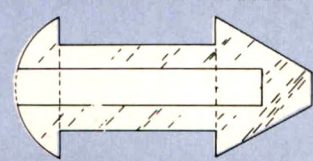
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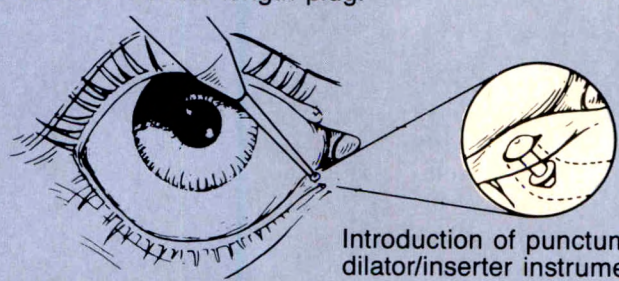
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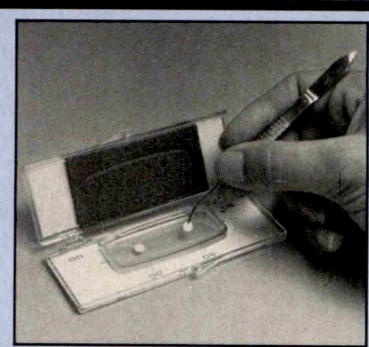
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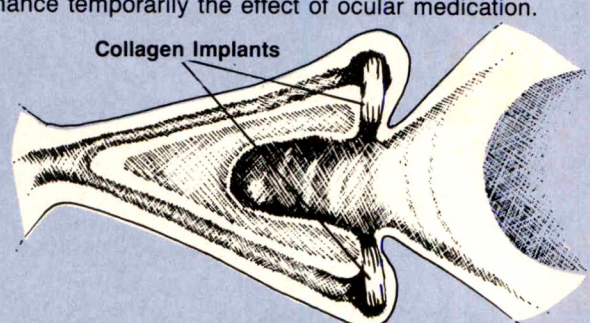
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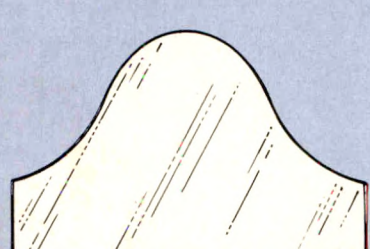
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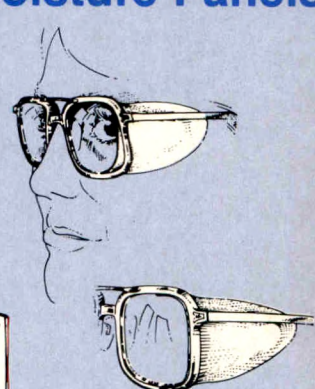
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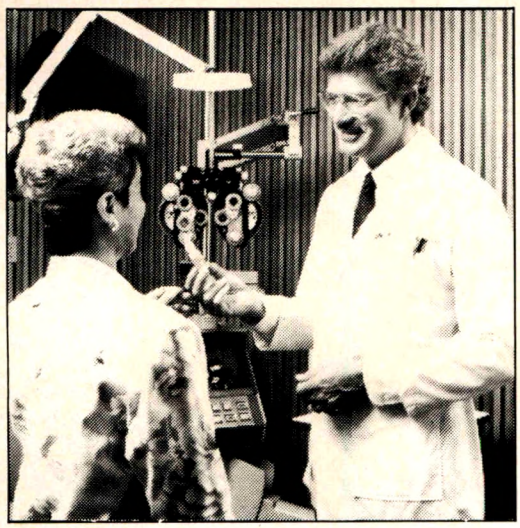
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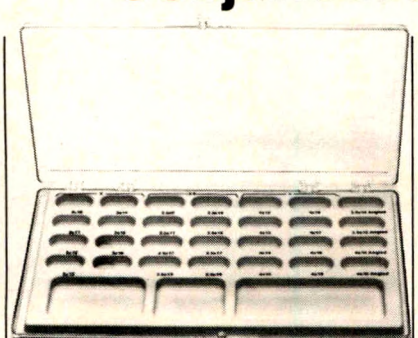
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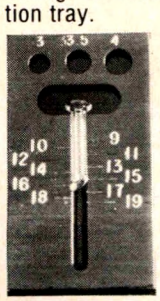
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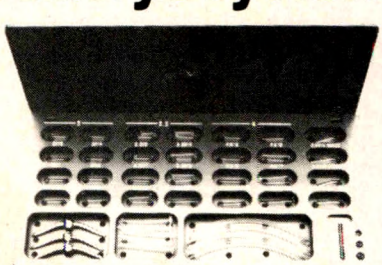
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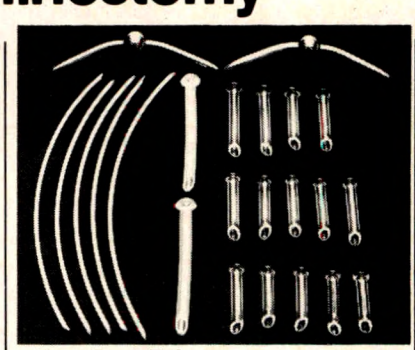
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If percentages are used, the numerical equivalents must be included, for example, Of 80 patients, 20 (25%) had retinitis pigmentosa.

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3. O'Connor, G. R.: Herpes zoster uveitis. In Kraus-Mackiw, E., and O'Connor, G. R. (eds.): Uveitis. Pathophysiology and Therapy. New York, Thieme-Stratton, 1983, pp. 56–65.

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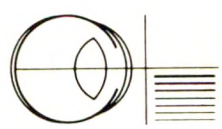
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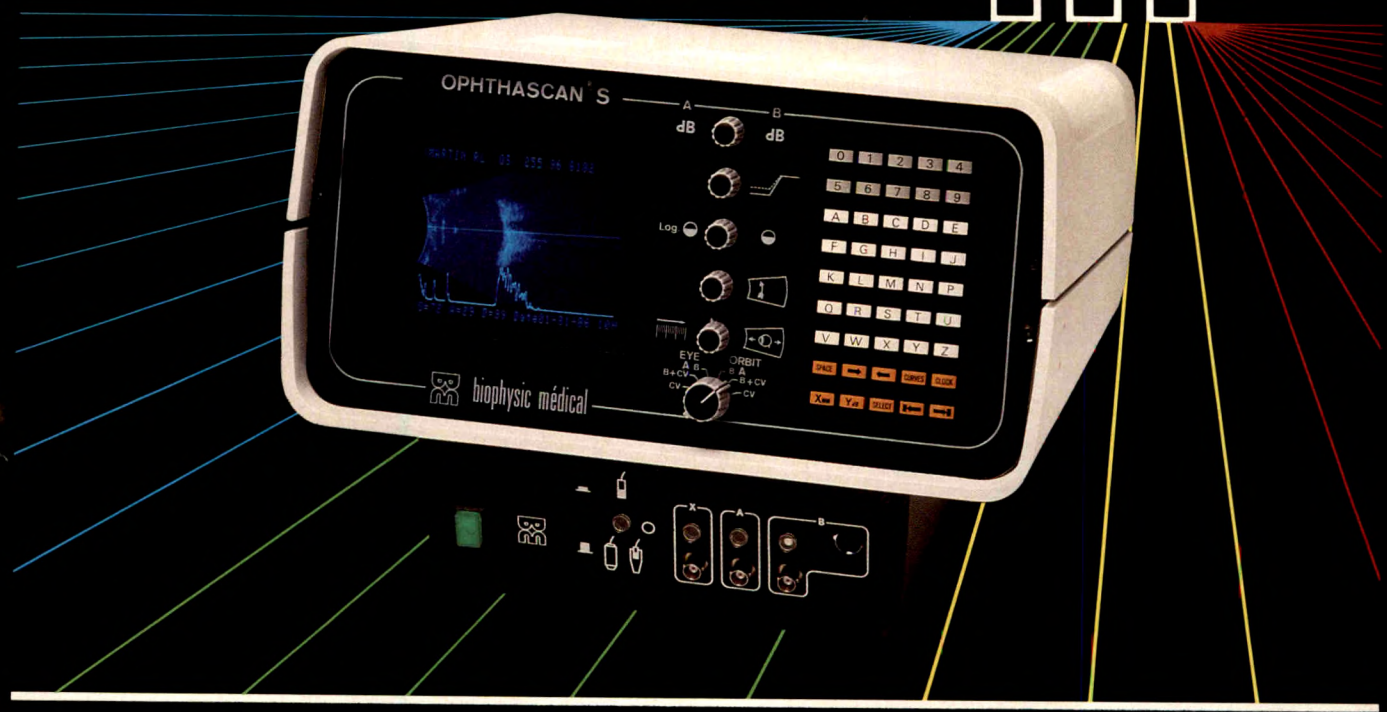
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Twin Vessels in von Hippel-Lindau Disease

Paul T. V. M. de Jong, M.D., Ruud J. F. Verkaart, M.D.,
Mies J. van de Vooren, M.D., Danielle F. Majoor-Krakauer, M.D.,
and Anton R. Wiegel, M.D.

We examined ten patients from three families with von Hippel-Lindau disease and 26 of their at-risk relatives for the presence of twin vessels, defined as a paired retinal arteriole and venule that are separated by less than the diameter of one venule and extend for a distance of more than one disk diameter. They were compared with 36 age- and sex-matched controls. Of the 36 subjects in the study group, 23 had twin vessels compared with two controls ($P < 10^{-6}$). Of the ten patients, nine (14 eyes) had twin vessels; no twin vessels were found in their controls ($P = 5.9 \times 10^{-5}$). Fourteen at-risk relatives and two of their controls had twin vessels ($P = 9.4 \times 10^{-4}$).

© American Journal of Ophthalmology 105:165–169, February, 1988

Pathogenesis and Therapy of Traction Detachment in Various Retinal Vascular Diseases

Robert Machemer, M.D., and John M. Williams, Sr., M.D.

We examined six patients with retinal vasculopathies (two cases each of angiomatosis retinae [von Hippel-Lindau disease], exudative vitreoretinopathy, and Coats' disease), who developed preretinal and vitreal membranes, retinal traction detachment, and exudation under the retina. The membranes consisted of a core of collagen of various diameter fibers, usually covered on both sides by cells that displayed glial cell characteristics. This study showed evidence of a common pathomechanism: exudation from diseased retinal vessels stimulates glial proliferation and collagen production resulting in preretinal and intravitreal membrane formation and traction detachment. This, in turn, allows exudate to reach the subretinal space where it is partially dehydrated. In our patients, the retina reattached spontaneously and exudates disappeared when traction was eliminated by vitreous surgery. Membrane formation did reoccur after vitrectomy if the vessels continued to leak, leading again to traction and subretinal exudation. Treatment consisted of surgical removal of vitreal and preretinal membranes and destruction of leaking vessels.

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HLA Typing in Birdshot Chorioretinopathy

H. A. Priem, M.D., A. Kijlstra, Ph.D., L. Noens, M.D., G. S. Baarsma, M.D.,
J. J. De Laey, M.D., and J. A. Oosterhuis, M.D.

We examined 49 patients with birdshot chorioretinopathy in whom HLA typing had been performed. Of these 49 patients, 47 (95.9%) had the HLA-A29 antigen. The HLA-B12 (B44) antigen was also significantly associated with the disease, but this antigen is known to be in linkage disequilibrium with the antigen HLA-A29. The HLA-A2 antigen was less frequent in patients with birdshot chorioretinopathy than in the control group of normal European individuals (20% as compared to 44.6%).

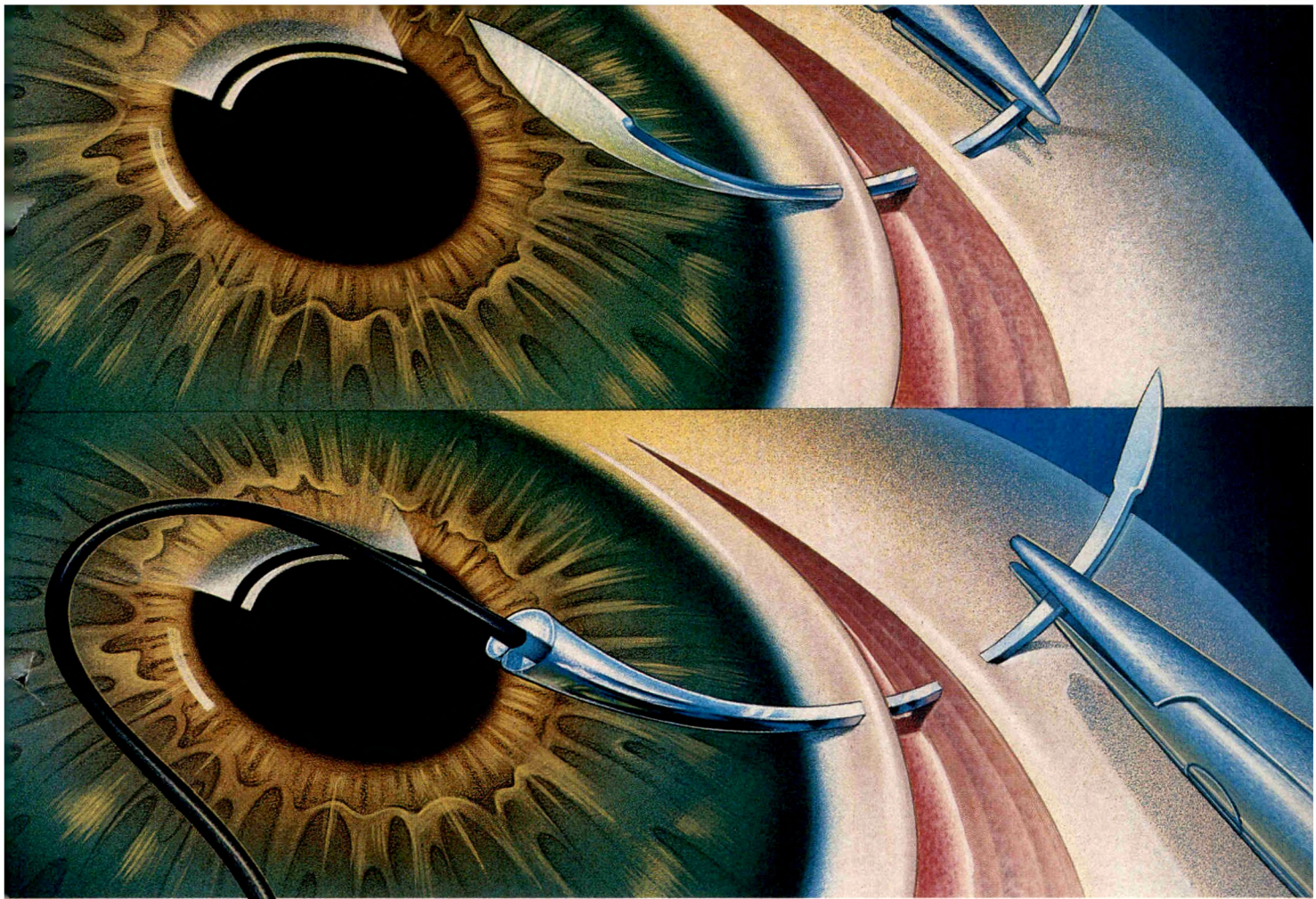
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The Diagnosis and Treatment of Bilateral Masked Superior Oblique Palsy

Burton J. Kushner, M.D.

I reviewed retrospectively the records of 147 consecutive patients who had superior oblique palsy. Of the 147 patients, 28 had bilateral superior oblique palsies, and in nine of the 28 the involvement was so asymmetric that the palsy in the lesser affected eye was either completely masked or almost masked preoperatively. Relying on preoperative diagnostic criteria such as the presence of bilateral objective torsion, cover testing in the oblique fields of gaze, size of the subjective cyclotropia, amount of the "V" shift, and subjective symptoms, all nine patients underwent bilateral surgery at the time of their initial operation and obtained satisfactory results. No patient was later found to have bilateral masked superior oblique palsy after unilateral surgery.

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Bacillus Keratitis Associated With Contaminated Contact Lens Care Systems

Paul B. Donzis, M.D., Bartly J. Mondino, M.D., and Barry A. Weissman, O.D.

We examined two soft contact lens wearers who developed keratitis associated with *Bacillus* contamination of their contact lens care systems. Patient 1 developed a corneal ulcer caused by *B. subtilis*, and Patient 2 demonstrated multiple, diffuse, punctate corneal epithelial opacities associated with *B. cereus* contamination in the contact lens and lens case compartment. The contact lens cases of both patients contained *Bacillus* spores that survived multiple heat disinfection treatments. Three different contact lens chemical disinfection systems used for the minimum recommended time failed to kill the *Bacillus* organisms.

© American Journal of Ophthalmology 105:195–197, February, 1988

Effects of Gentamicin on Healing of Transdifferentiating Conjunctival Epithelium in Rabbit Eyes

Eduardo Alfonso, M.D., Kenneth R. Kenyon, M.D., Donald J. D'Amico, M.D., Amanda M. Saulenas, B.S., and Daniel M. Albert, M.D.

We examined the effects of commercially prepared gentamicin, a wide-spectrum topical antibiotic, on the healing of epithelial defects of the rabbit cornea. Abrasions were created by: (1) removing the corneal epithelium and 3 mm of the conjunctival epithelium (Group 1); and (2) producing the same initial trauma and subsequently removing the central 8 mm of epithelium 28 days after initial healing (Group 2). The complete healing of the large corneal and conjunctival epithelial defects was not delayed when gentamicin solution was used four times a day (Group 1). When the healed epithelium was reinjured while transdifferentiating from conjunctival to corneal epithelium (day 28, Group 2), treatment with the gentamicin solution and its vehicle, both containing benzalkonium chloride, delayed epithelial healing significantly compared with treatment with saline ($P < .01$).

© American Journal of Ophthalmology 105:198–202, February, 1988

Absence of *Chlamydia* in Trachomatous Lacrimal Sacs

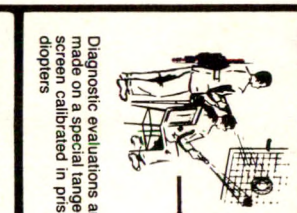
Charles D. Rice, M.D., and Robert C. Kersten, M.D.

We performed lacrimal sac biopsies in 35 patients who underwent dacryocystorhinostomies in Saudi Arabia. The nasolacrimal duct obstructions were presumably secondary to trachoma in 22 cases and unknown in the remaining 13 cases. Lacrimal sac specimens were submitted for routine histopathologic examination and the direct-smear fluorescent antibody test. All specimens were negative for chlamydia. Possible reasons for the low detection rate of chlamydia in the trachomatous group were the frequent finding of clinically inactive disease, common canalicular obstruction, and loss of the epithelial lining in the lacrimal sac.

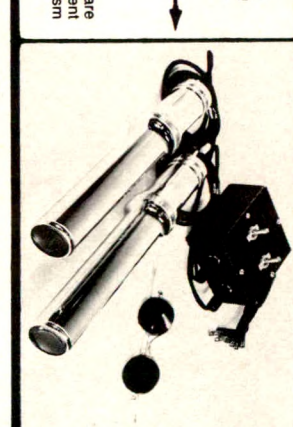
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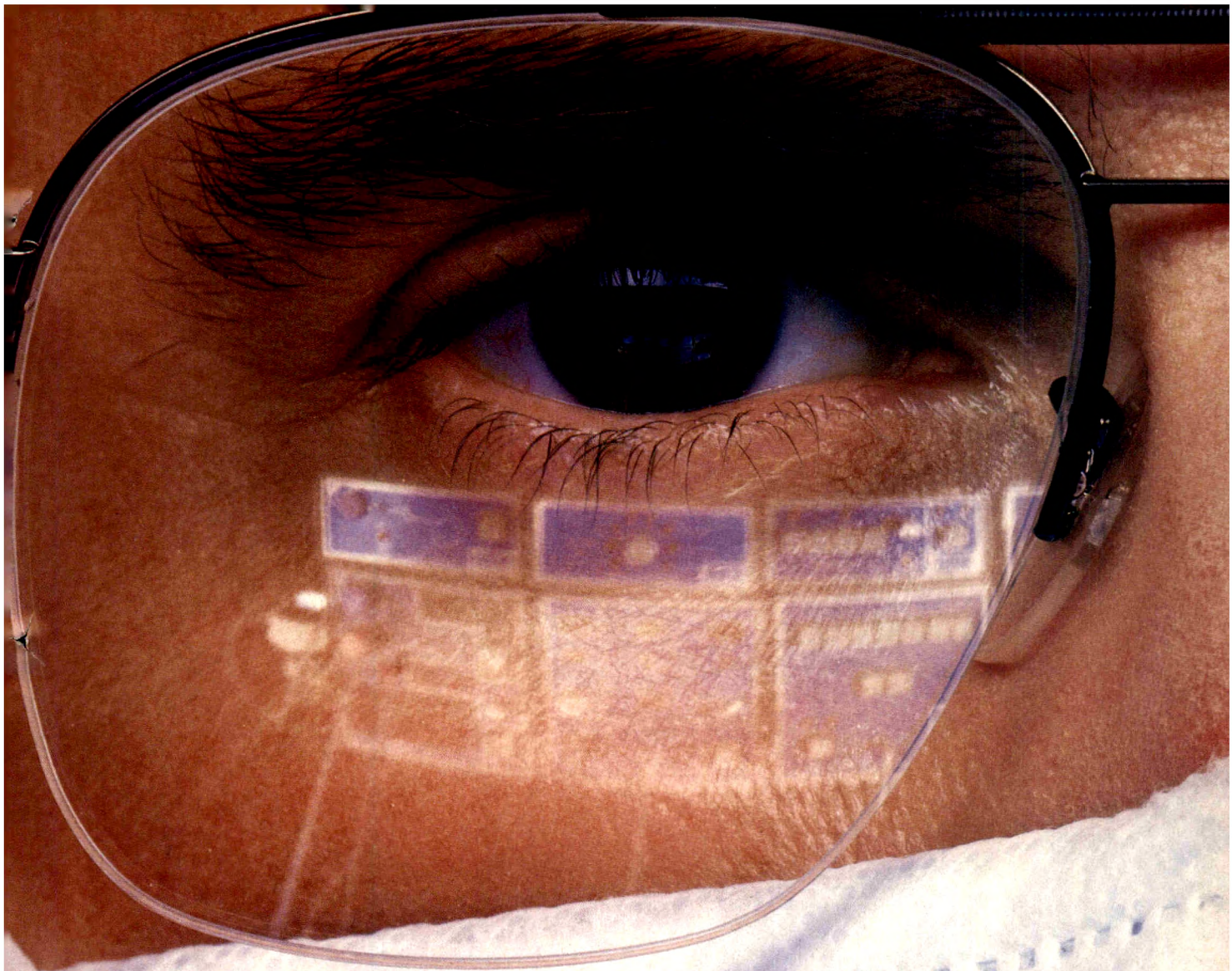
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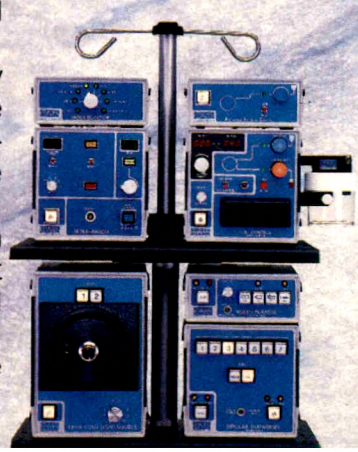
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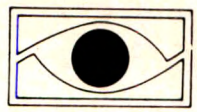
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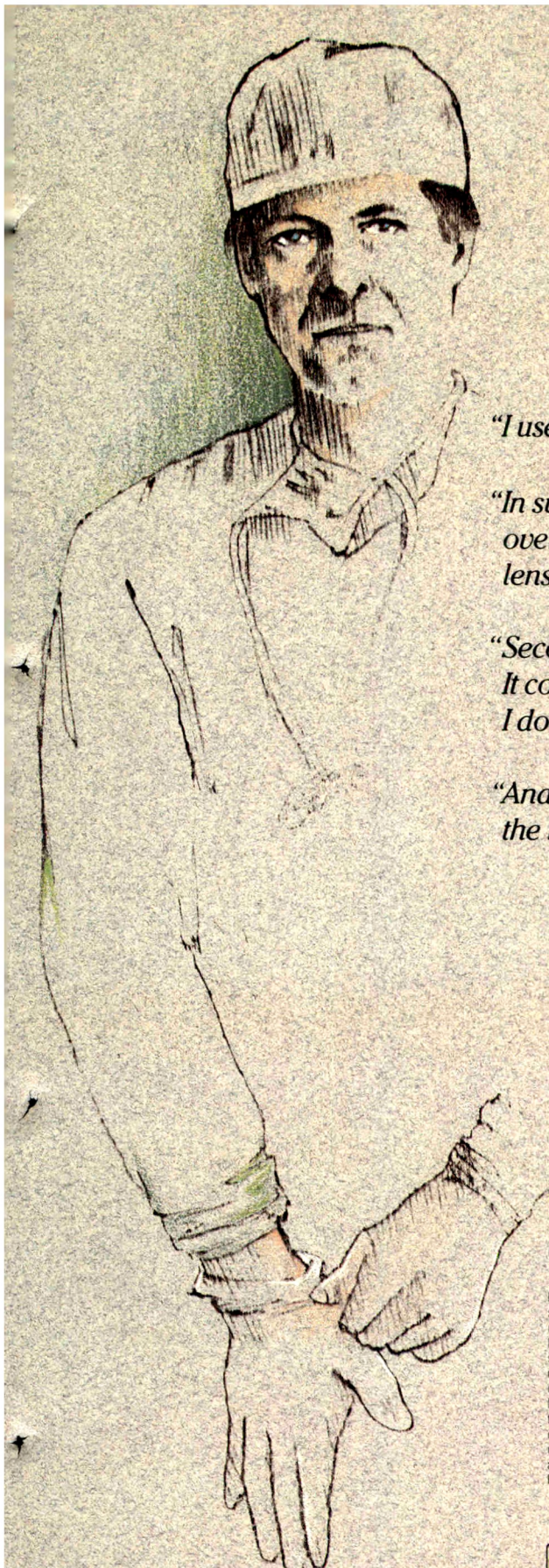
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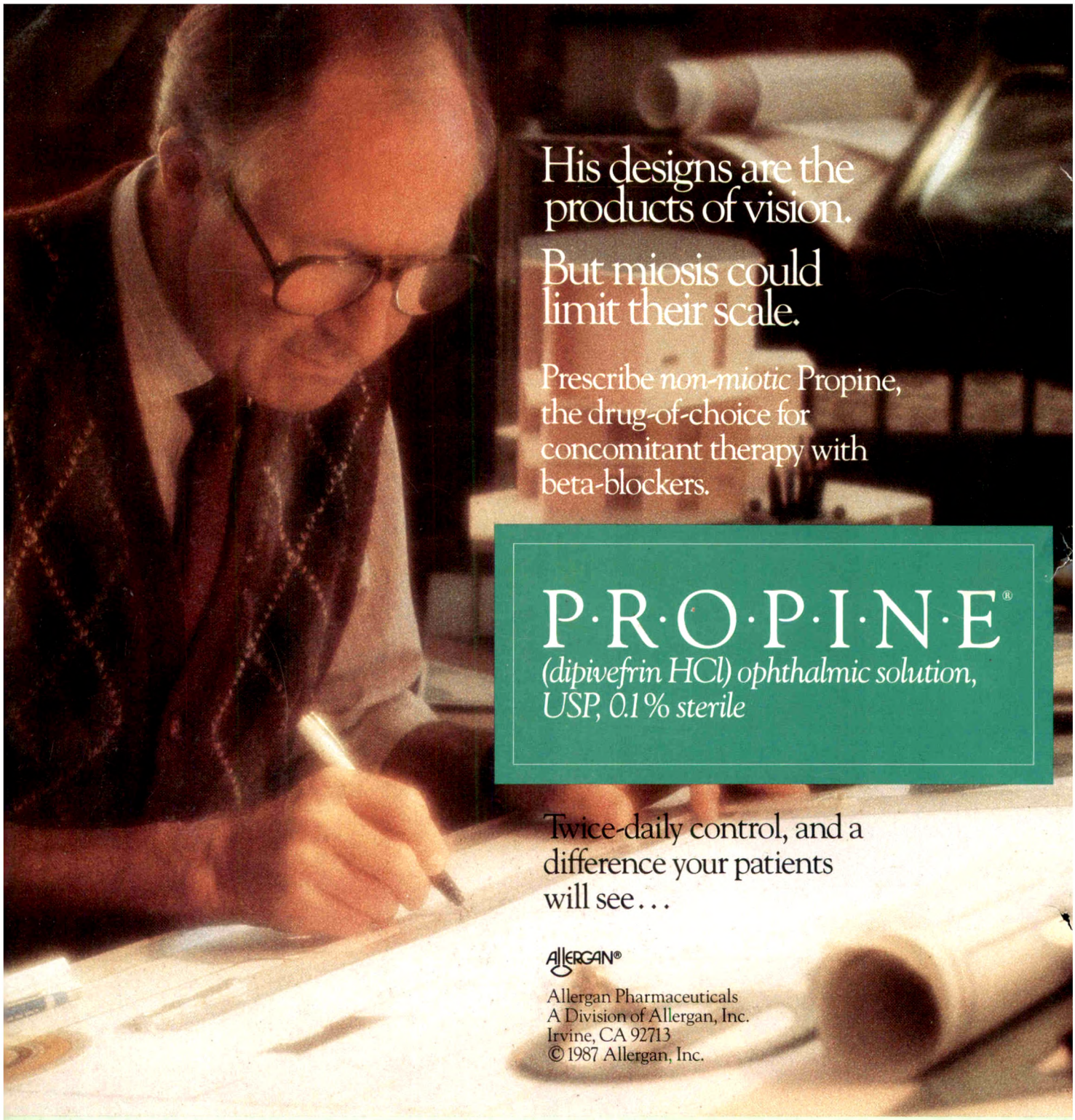
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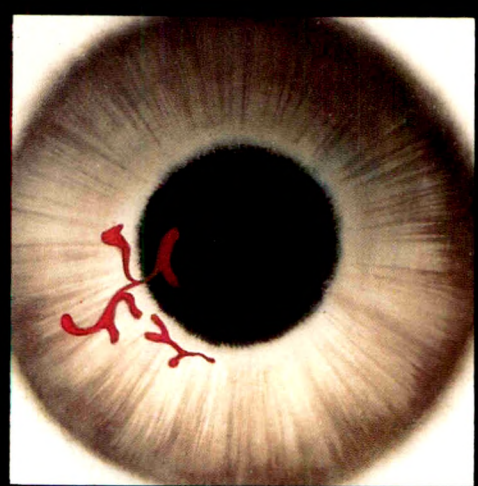
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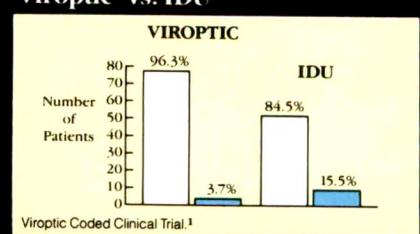
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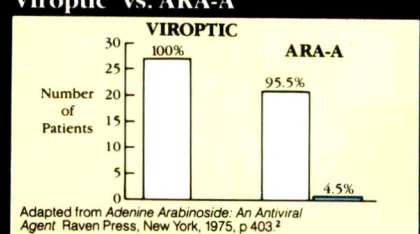
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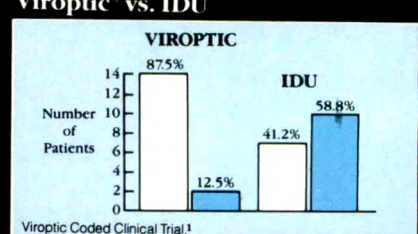
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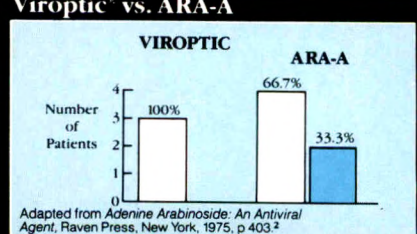
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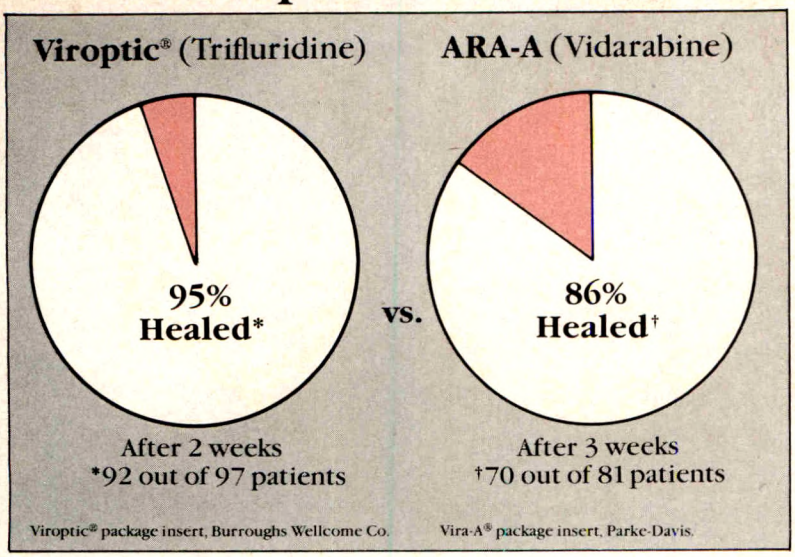
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References

1. Data on file, Medical Division, Burroughs Wellcome Co.
2. McKinnon JR, McGill JI, Jones BR: A coded clinical evaluation of adenine arabinoside and trifluorothymidine in the treatment of ulcerative herpetic keratitis, in Pavan-Langston D, Buchanan RA, Alford CA Jr (eds): *Adenine Arabinoside: An Antiviral Agent*, Raven Press, New York, 1975, p 403.
3. Kaufman HE, Centifanto-Fitzgerald YM, Varnell ED: Herpes simplex keratitis. *Ophthalmology* 1983;90:700-706.

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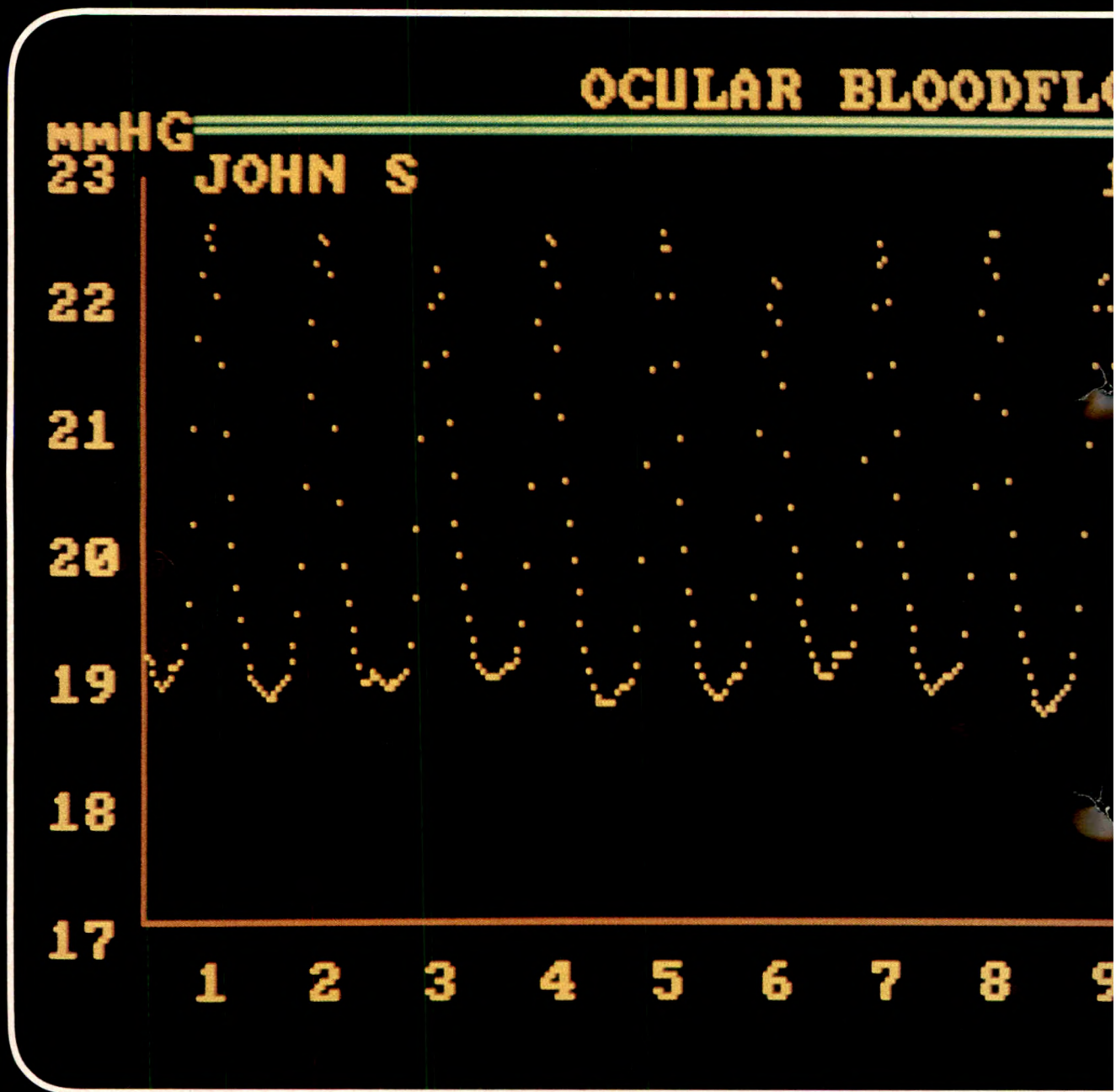
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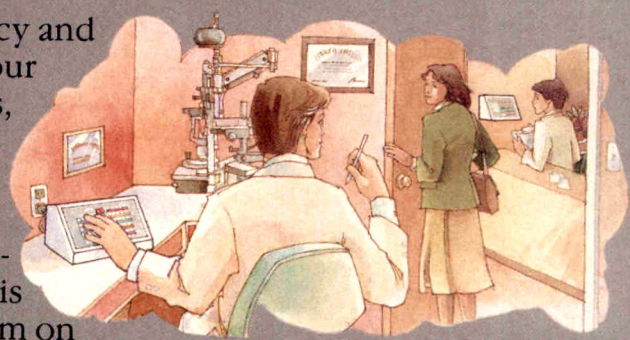


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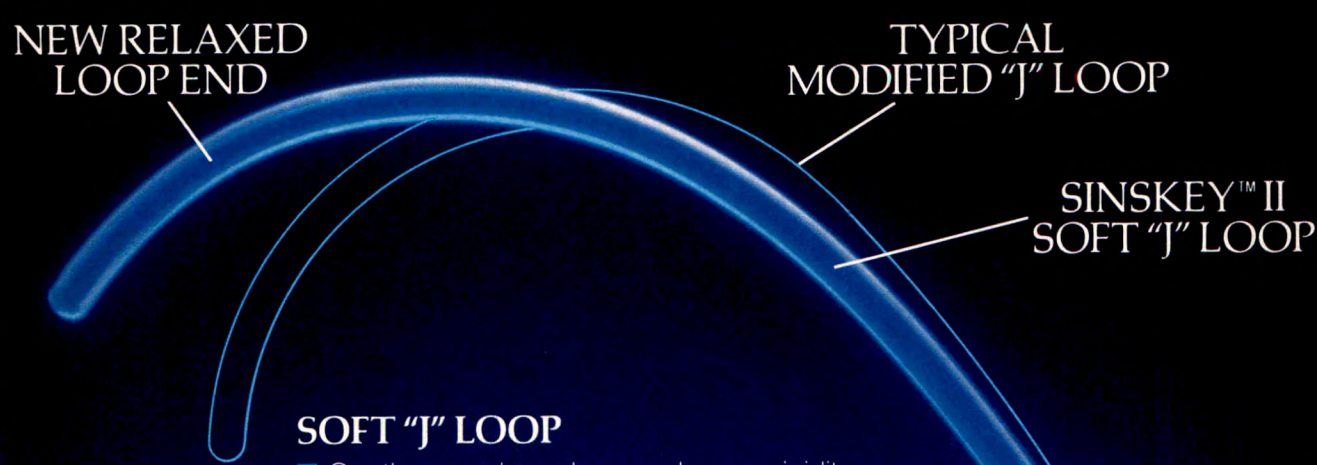
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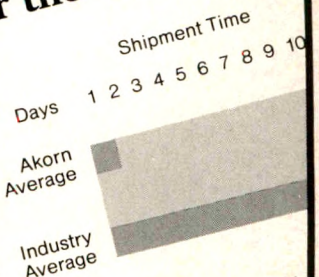
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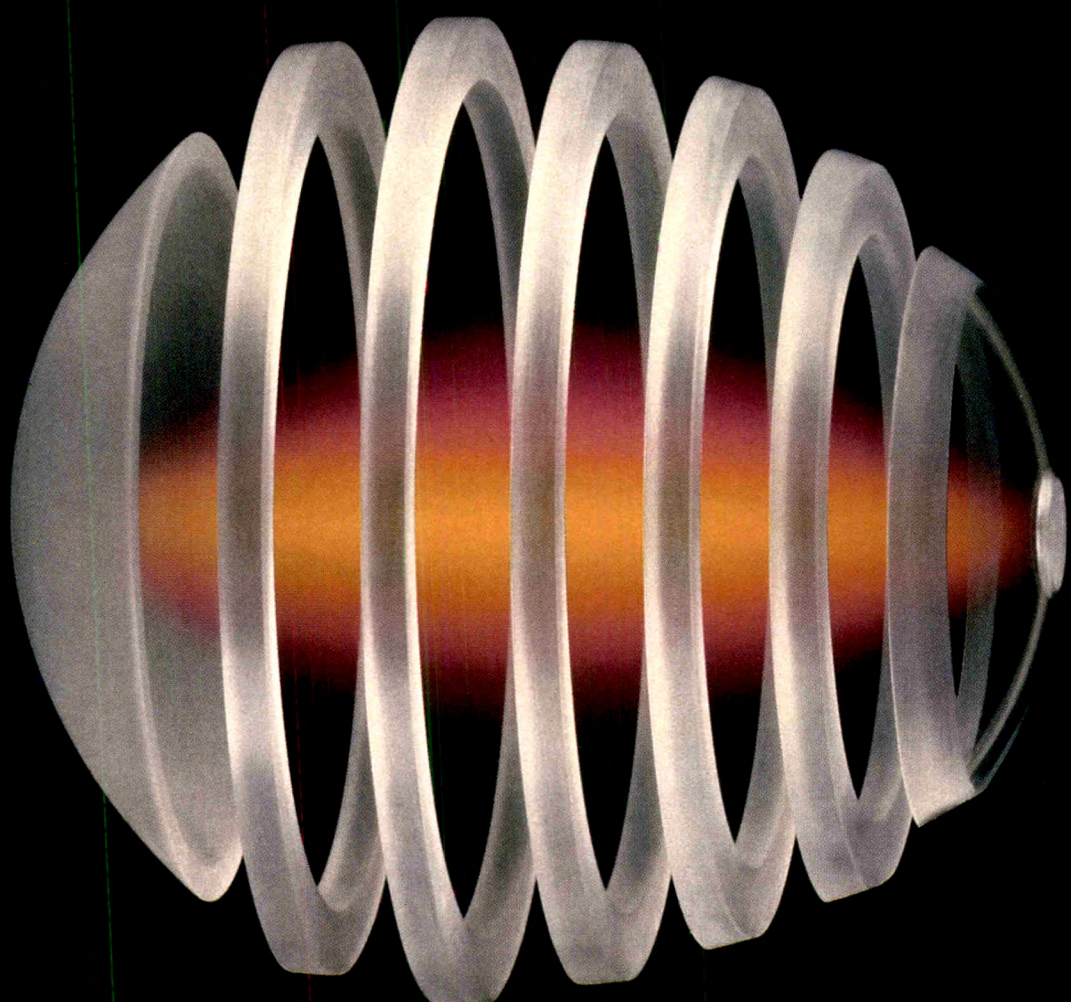
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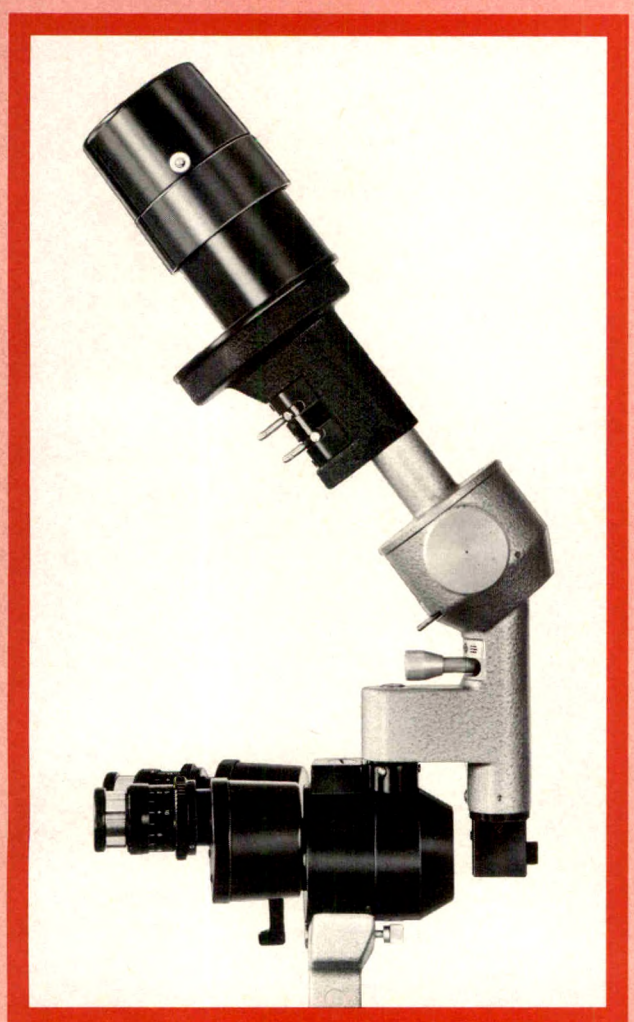
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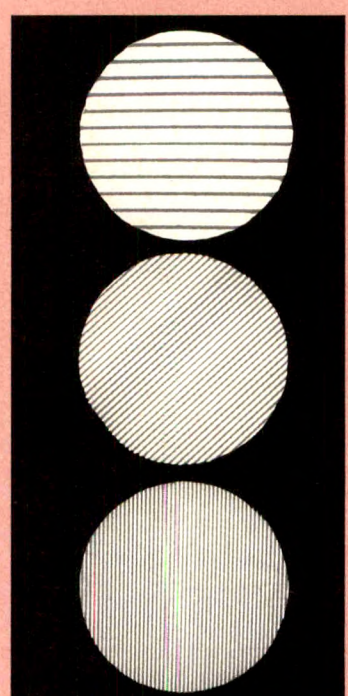
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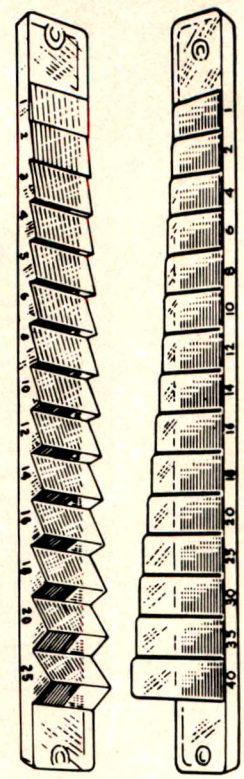
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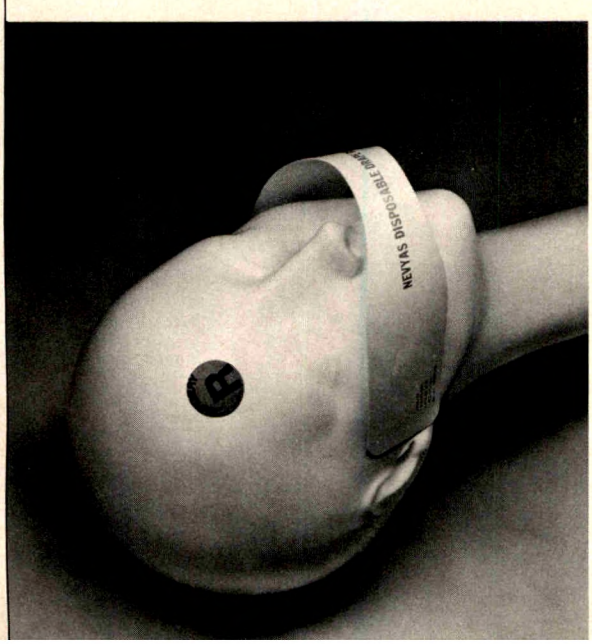
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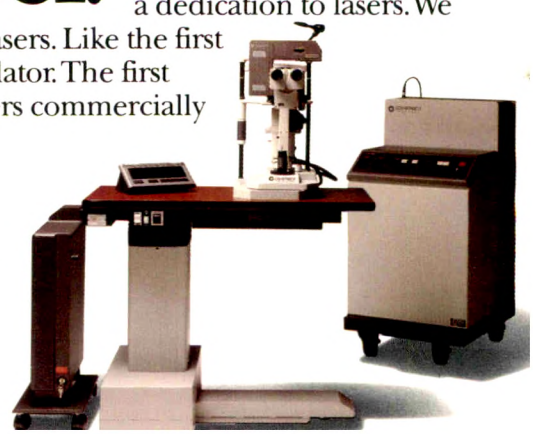
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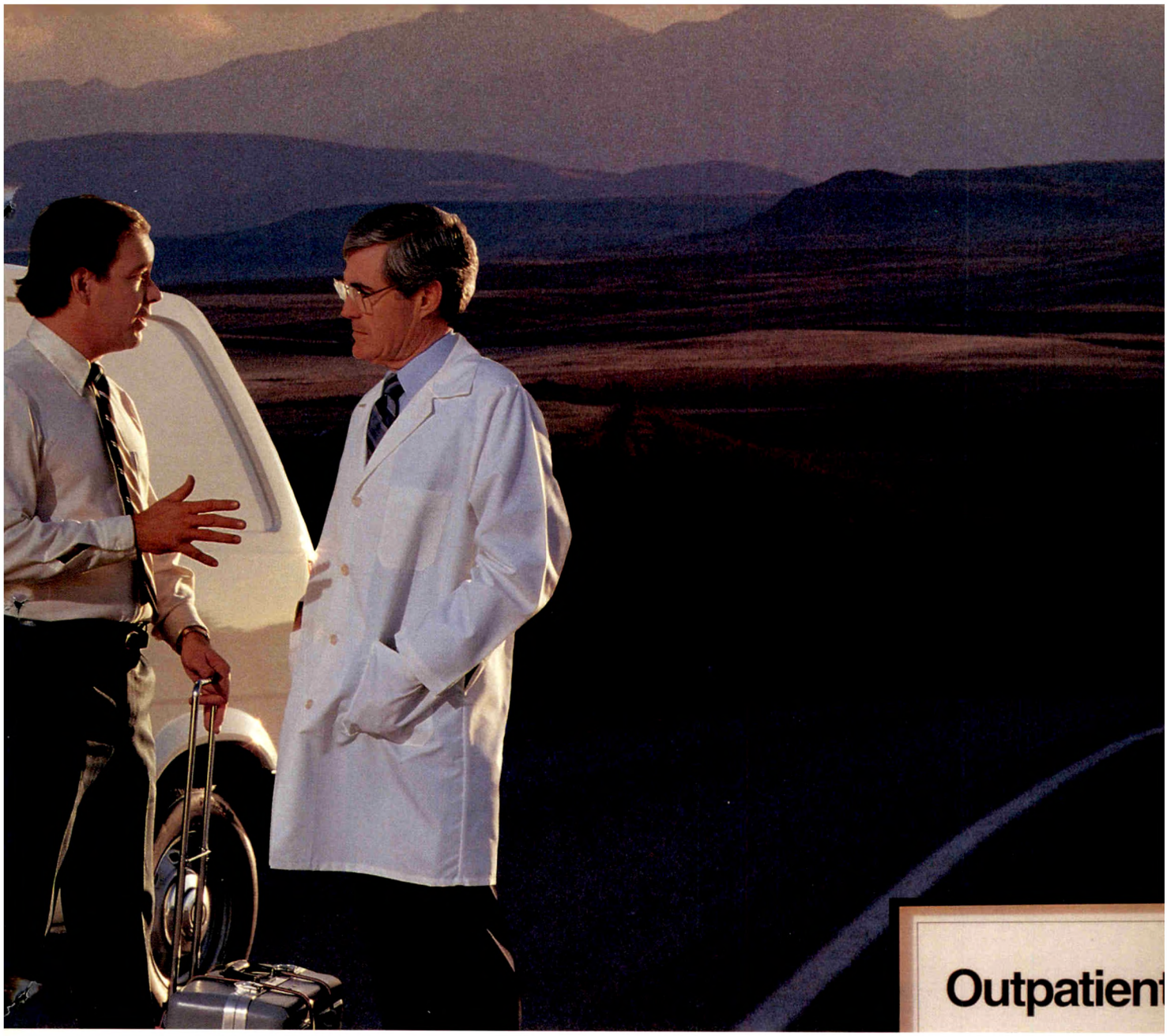
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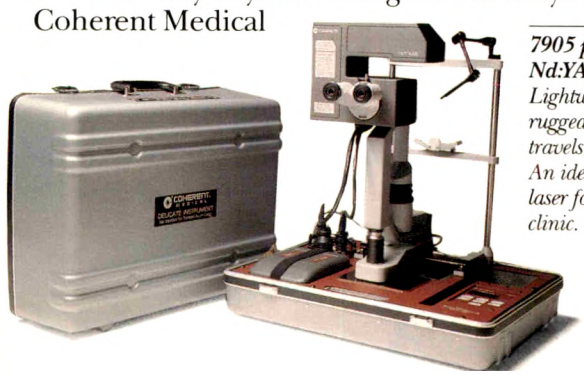


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This two-day seminar will address current developments in the fields of pediatric ophthalmology, strabismus, and ocular genetics. Topics to be emphasized are the eye in infancy, common ocular problems in children, the use of botulinum toxin in strabismus treatment, and the diagnosis and treatment of congenital ocular opacities. Ample opportunity will be provided for questions and discussion.

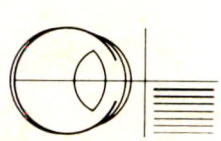
A dinner dance honoring Dr. Jampolsky and course faculty will be held at the Beverly Hills Hotel on Friday evening, April 22, 1987.

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Aldose Reductase Inhibitor (CT-112) Eyedrops for Diabetic Corneal Epitheliopathy

Yuichi Ohashi, M.D., Mamoru Matsuda, M.D., Hisashi Hosotani, M.D, Yasuo Tano, M.D., Ichiro Ishimoto, M.D., Masakatsu Fukuda, M.D., and Reizo Manabe, M.D.

We treated two diabetic patients with corneal epithelial disorder that resisted conventional medical therapy with topical CT-112 (5-[3-ethoxy-4-pentyloxyphenyl]-2,4-thiazolidinedione), a newly synthesized aldose reductase inhibitor. One patient had developed recurrent corneal erosion after vitrectomy and the other had spontaneously developed superficial punctate keratopathy. The corneal lesion in each patient responded to topical CT-112 in two to four weeks and was almost cleared within two months. A similar corneal lesion reccurred in both patients soon after CT-112 was discontinued, but it disappeared again when the drug was resumed.

© American Journal of Ophthalmology 105:233–238, March, 1988

Fortified Antibiotic Ointment in Bacterial Keratitis

Robert A. Hyndiuk, M.D., Daniel N. Skorich, M.D., Starkey D. Davis, M.D., Larrie D. Sarff, M.D., Kathy Divine, M.S., and Eileen Burd, M.S.

We conducted experiments to determine the effectiveness of fortified antibiotic ointment in the treatment of *Pseudomonas* keratitis in rabbits. We evaluated gentamicin ointment (3, 10, 20, and 40 mg/g), gentamicin solution (3 and 10 mg/ml), and placebo, each given every 30 minutes. We also examined the effectiveness of fortified ointment given in extended treatment intervals. In short-term trials, commercial-strength gentamicin solution (3 mg/ml) was therapeutically superior ($P < .001$) to commercial-strength gentamicin ointment (3 mg/g) in reducing corneal bacterial colony counts. No significant difference in antimicrobial effect was noted between fortified gentamicin ointment and fortified gentamicin solution at 30-minute treatment intervals. Fortified gentamicin ointment reduced colony counts even at extended treatment intervals of up to four hours in a severe keratitis model.

© American Journal of Ophthalmology 105:239–243, March, 1988

Use of Split-Thickness Dermal Graft in the Surgical Treatment of Corneal and Scleral Defects

Joseph A. Mauriello, Jr., M.D., Philip M. Fiore, M.D., Kathryn S. Pokorny, Ph.D., and Donald J. Cinotti, M.D.

We used split-thickness dermal grafts for the surgical treatment of corneal and scleral perforations in two patients and obtained excellent results. Patient 1 had severe lye burns and bilateral corneal perforations and Patient 2 had scleromalacia perforans. The dermal graft self-epithelializes and, thus, does not need to be covered by conjunctiva; is supple, without the bulkiness of other materials, particularly cartilage and periosteum; is hearty and flourishes on avascular surfaces such as cornea and sclera; has good tensile strength; and is autogenous.

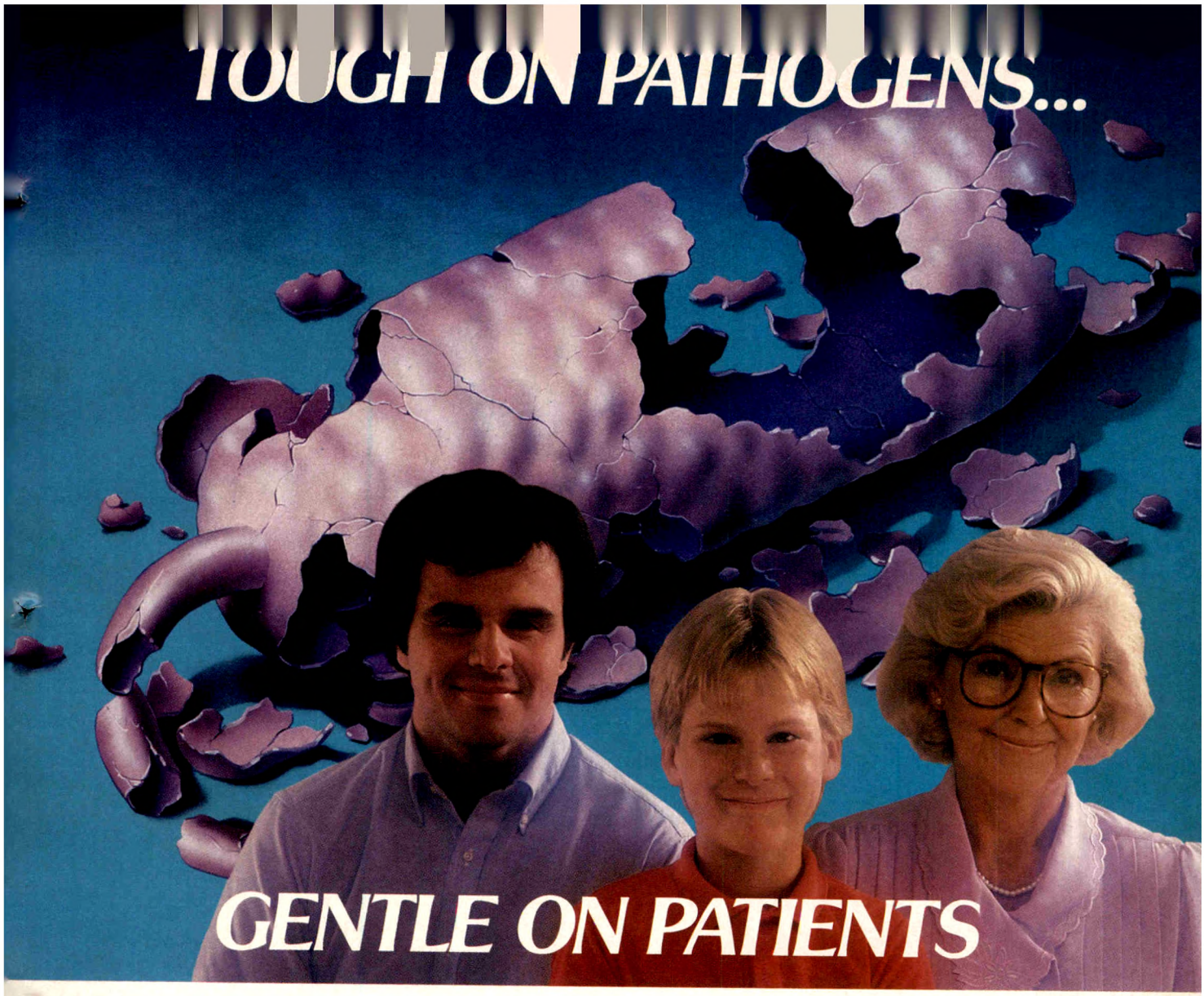
© American Journal of Ophthalmology 105:244–247, March, 1988

Long-Term Corneal Endothelial Changes After Intraocular Lens Implantation

Mamoru Matsuda, M.D., Kensaku Miyake, M.D., and Masamaru Inaba, M.D.

We studied the morphologic characteristics of the corneal endothelium in a series of patients who had undergone phacoemulsification with intraocular lens implantation performed by one surgeon. Specular microscopy and computer-assisted morphometry were performed preoperatively and three years after surgery. Nineteen eyes that received posterior chamber lenses with intracapsular fixation had a mean endothelial cell loss of 18.1%, without any significant change in cell size (polymegethism) or shape variability (pleomorphism). Implantation of anterior chamber lenses with the posterior capsule left intact (18 eyes) caused a similar degree of cell loss (23.5%) but caused marked polymegethism and pleomorphism of the cells. Endothelial cell loss (28.5%) and morphologic changes were greatest in five eyes that received anterior chamber lenses because of a rupture of the posterior capsule.

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Each gram of ointment contains: Tobramycin 0.3% (3 mg/g), Mineral Oil, White Petrolatum, and Chlorobutanol (0.5%) as a preservative. DM-00
Tobramycin is a water-soluble aminoglycoside antibiotic active against a wide variety of gram-negative and gram-positive ophthalmic pathogens.

CLINICAL PHARMACOLOGY:
In Vitro Data: In vitro studies have demonstrated tobramycin is active against susceptible strains of the following microorganisms:
Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.
Streptococci, including some of the Group A–betahemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae*.
Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis (indole-negative) and indole-positive. *Proteus* species, *Haemophilus influenzae* and *H. aegyptius, Moraxella lacunata,* and *Acinetobacter calcoaceticus (Herellea vaginacola)* and some *Neisseria* species. Bacterial susceptibility studies demonstrate that in some cases, microorganisms resistant to gentamicin retain susceptibility to tobramycin. A significant bacterial population resistant to tobramycin has not yet emerged; however, bacterial resistance may develop upon prolonged use.

INDICATIONS AND USAGE: TOBREX is a topical antibiotic indicated in the treatment of external infections of the eye and its adnexa caused by susceptible bacteria. Appropriate monitoring of bacterial response to topical antibiotic therapy should accompany the use of TOBREX. Clinical studies have shown tobramycin to be safe and effective for use in children.

CONTRAINDICATIONS: TOBREX Ophthalmic Solution and Ointment are contraindicated in patients with known hypersensitivity to any of their components.

WARNINGS: NOT FOR INJECTION INTO THE EYE. Sensitivity to topically applied aminoglycosides may occur in some patients. If a sensitivity reaction to TOBREX® occurs, discontinue use.

PRECAUTIONS: As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. Ophthalmic ointments may retard corneal wound healing.
Pregnancy Category B. Reproduction studies in three types of animals at doses up to thirty-three times the normal human systemic dose have revealed no evidence of impaired fertility or harm to the fetus due to tobramycin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers: Because of the potential for adverse reactions in nursing infants from TOBREX, a decision should be made whether to discontinue nursing the infant or discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS: The most frequent adverse reactions to TOBREX Ophthalmic Solution and Ointment are localized ocular toxicity and hypersensitivity, including lid itching and swelling, and conjunctival erythema. These reactions occur in less than three of 100 patients treated with TOBREX. Similar reactions may occur with the topical use of other aminoglycoside antibiotics. Other adverse reactions have not been reported from TOBREX therapy; however, if topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration.
In clinical trials, TOBREX Ophthalmic Ointment produced significantly fewer adverse reactions (3.7%) than did Garamycin Ophthalmic Ointment (10.6%).

OVERDOSAGE: Clinically apparent signs and symptoms of an overdose of TOBREX Ophthalmic Solution or Ointment (punctate keratitis, erythema, increased lacrimation, edema and lid itching) may be similar to adverse reaction effects seen in some patients.

DOSAGE AND ADMINISTRATION: *SOLUTION:* In mild to moderate disease, instill one or two drops into the affected eye(s) every four hours. In severe infections, instill two drops into the eye(s) hourly until improvement, following which treatment should be reduced prior to discontinuation.
OINTMENT: In mild to moderate disease, apply a half-inch ribbon into the affected eye(s) two or three times per day. In severe infections, instill a half-inch ribbon into the affected eye(s) every three to four hours until improvement, following which treatment should be reduced prior to discontinuation.
How to Apply TOBREX® Ointment
1. Tilt your head back.
2. Place a finger on your cheek just under your eye and gently pull down until a "V" pocket is formed between your eyeball and your lower lid.
3. Place a small amount (about ½ inch) of TOBREX in the "V" pocket. Do not let the tip of the tube touch your eye.
4. Look downward before closing your eye.

TOBREX Ointment may be used in conjunction with TOBREX Solution.

HOW SUPPLIED: STERILE solution in 5 ml Drop-Tainer® dispenser (NDC 0998-0643-05), containing tobramycin 0.3% (3 mg/ml) and STERILE ointment in 3.5 g ophthalmic tube (NDC 0065-0644-35), containing tobramycin 0.3% (3 mg/g).
STORAGE: Store at 8°-27°C (46°-80°F).
298251

References:

1. Bac-Data Bacteriologic Reports, Bac-Data Medical Information Systems Inc.
2. Data on file, Alcon Laboratories, Inc.

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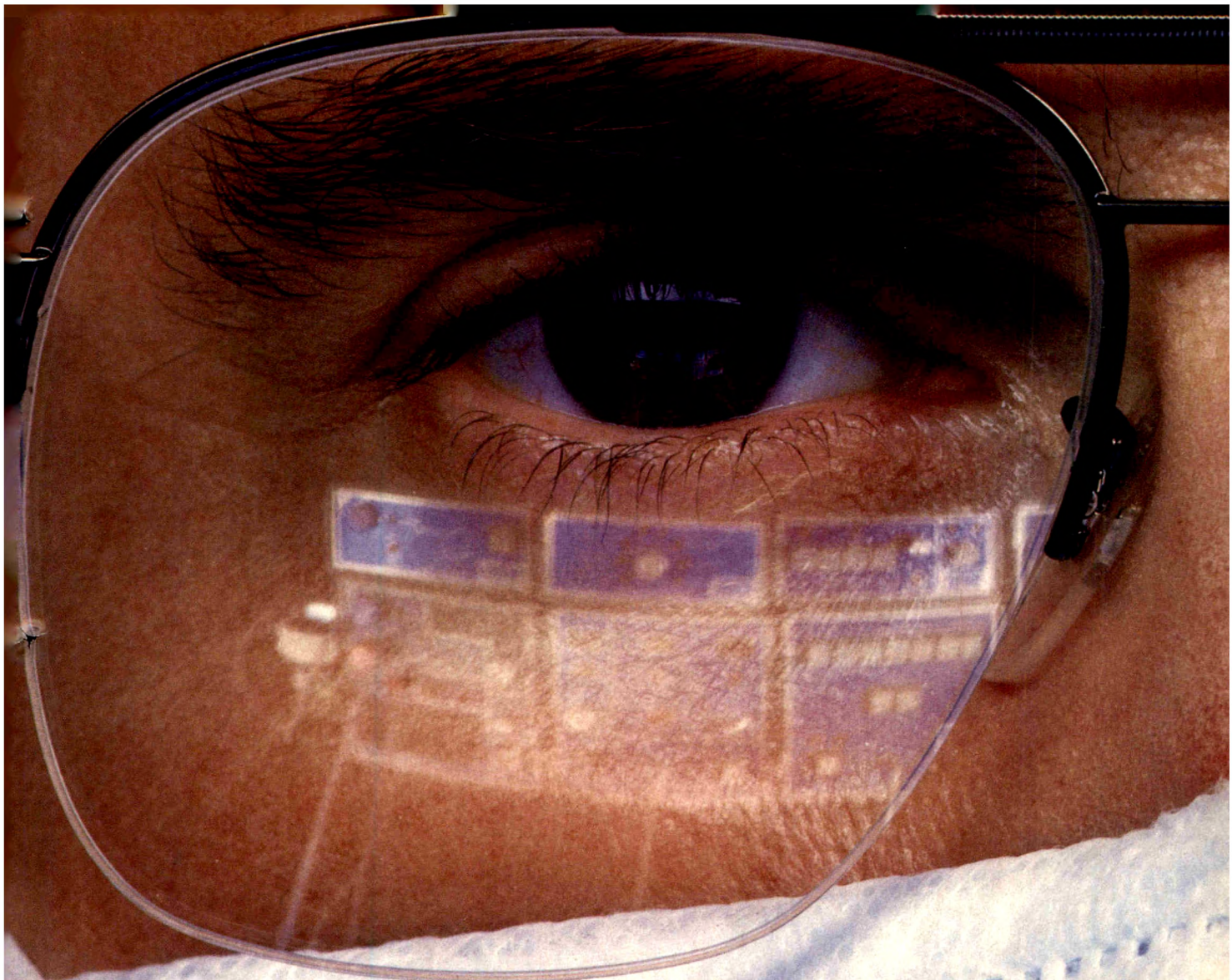
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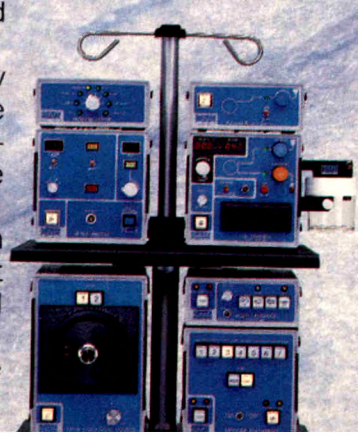
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British Journal of Ophthalmology February 1988 Vol. 72 No. 2

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Healon® (sodium hyaluronate)

Summary of Product Information

USES

Healon® is indicated for use as a surgical aid in cataract extraction (intra- and extracapsular), IOL implantation, corneal transplant, glaucoma filtration and retinal attachment surgery.

In surgical procedures in the anterior segment of the eye, instillation of Healon® serves to maintain a deep anterior chamber during surgery, allowing for efficient manipulation with less trauma to the corneal endothelium and other surrounding tissues.

Furthermore, its viscoelasticity helps to push back the vitreous face and prevent formation of a postoperative flat chamber.

In posterior segment surgery Healon® serves as a surgical aid to gently separate, maneuver and hold tissues. Healon® creates a clear field of vision thereby facilitating intra- and postoperative inspection of the retina and photocoagulation.

CONTRAINDICATIONS

At present there are no known contraindications to the use of Healon® when used as recommended.

PRECAUTIONS

Those normally associated with the surgical procedure being performed.

Overfilling the anterior or posterior segment of the eye with Healon® may cause increased intraocular pressure, glaucoma, or other ocular damage.

Postoperative intraocular pressure may also be elevated as a result of pre-existing glaucoma, compromised outflow, and by operative procedures and sequelae thereto, including enzymatic zonulysis, absence of an iridectomy, trauma to filtration structures, and by blood and lenticular remnants in the anterior chamber. Since the exact role of these factors is difficult to predict in any individual case, the following precautions are recommended:

- Don't overfill the eye chambers with Healon® (except in glaucoma surgery—see Application section).
- In posterior segment procedures in aphakic diabetic patients special care should be exercised to avoid using large amounts of Healon®
- Remove some of the Healon® by irrigation and/or aspiration at the close of surgery (except in glaucoma surgery—see Application section).
- Carefully monitor intraocular pressure, especially during the immediate postoperative period. If significant rises are observed, treat with appropriate therapy.

Care should be taken to avoid trapping air bubbles behind Healon®

Because Healon® is a highly purified fraction extracted from avian tissues and is known to contain minute amounts of protein, the physician should be aware of potential risks of the type that can occur with the injection of any biological material.

Because of reports of an occasional release of minute rubber particles, presumably formed when the diaphragm is punctured, the physician should be aware of this potential problem. Express a small amount of Healon® from the syringe prior to use, and carefully examine the remainder as it is injected.

Avoid reuse of cannulas. If reuse becomes necessary, rinse cannula thoroughly with sterile distilled water.

Sporadic reports have been received indicating that Healon® may become "cloudy" or form a slight precipitate following instillation into the eye. The clinical significance of these reports, if any, is not known since the majority received to date do not indicate any harmful effects on ocular tissues. The physician should be aware of this phenomenon and, should it be observed, remove the cloudy or precipitated material by irrigation and/or aspiration.

In vitro laboratory studies suggest that this phenomenon may be related to interactions with certain concomitantly administered ophthalmic medications.

Use only if solution is clear.

ADVERSE REACTIONS

Healon® is extremely well tolerated after injection into human eyes. A transient rise of intraocular pressure postoperatively has been reported in some cases.

In posterior segment surgery intraocular pressure rises have been reported in some patients, especially in aphakic diabetics, after injection of large amounts of Healon®

Rarely, postoperative inflammatory reactions (iritis, hypopyon) as well as incidents of corneal edema and corneal decompensation have been reported. Their relationship to Healon® has not been established.

HOW SUPPLIED

Healon® is a sterile, nonpyrogenic, viscoelastic preparation supplied in disposable glass syringes, delivering 2.0 ml, 0.75 ml, 0.55 ml or 0.4 ml sodium hyaluronate (10 mg/ml) dissolved in physiological sodium chloride-phosphate buffer (pH 7.0-7.5). Each ml of Healon® contains 10 mg of sodium hyaluronate, 8.5 mg of sodium chloride, 0.28 mg of disodium hydrogen phosphate dihydrate, 0.04 mg of sodium dihydrogen phosphate hydrate and q.s. water for injection U.S.P. Healon® syringes are terminally sterilized and aseptically packaged. A sterile single-use, 27-gauge cannula is enclosed in the 0.4-ml, 0.55-ml, and 0.75-ml boxes.

Refrigerated Healon® should be allowed to attain room temperature (approximately 30 minutes) prior to use.

For intraocular use.
Store at 2—8°C.
Protect from freezing.
Protect from light.

CAUTION

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Revised: January 1988
Healon is covered by
U.S. patent 4,141,973,1979

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Juan J. Arensten, M.D.
Elisabeth J. Cohen, M.D.
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Michael A. Naidoff, M.D.
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Program Chairman: Juan J. Arentsen, M.D.

CME Credits:
AMA Category I (11 Hours)

Further Information:
Wills Eye Hospital
Department of Continuing Medical Education
9th & Walnut Streets
Philadelphia, PA 19107
Ms. Lucia M. Manes, Conference Coordinator
215-928-3378

The Department of Ophthalmology University of California School of Medicine San Francisco, California

presents

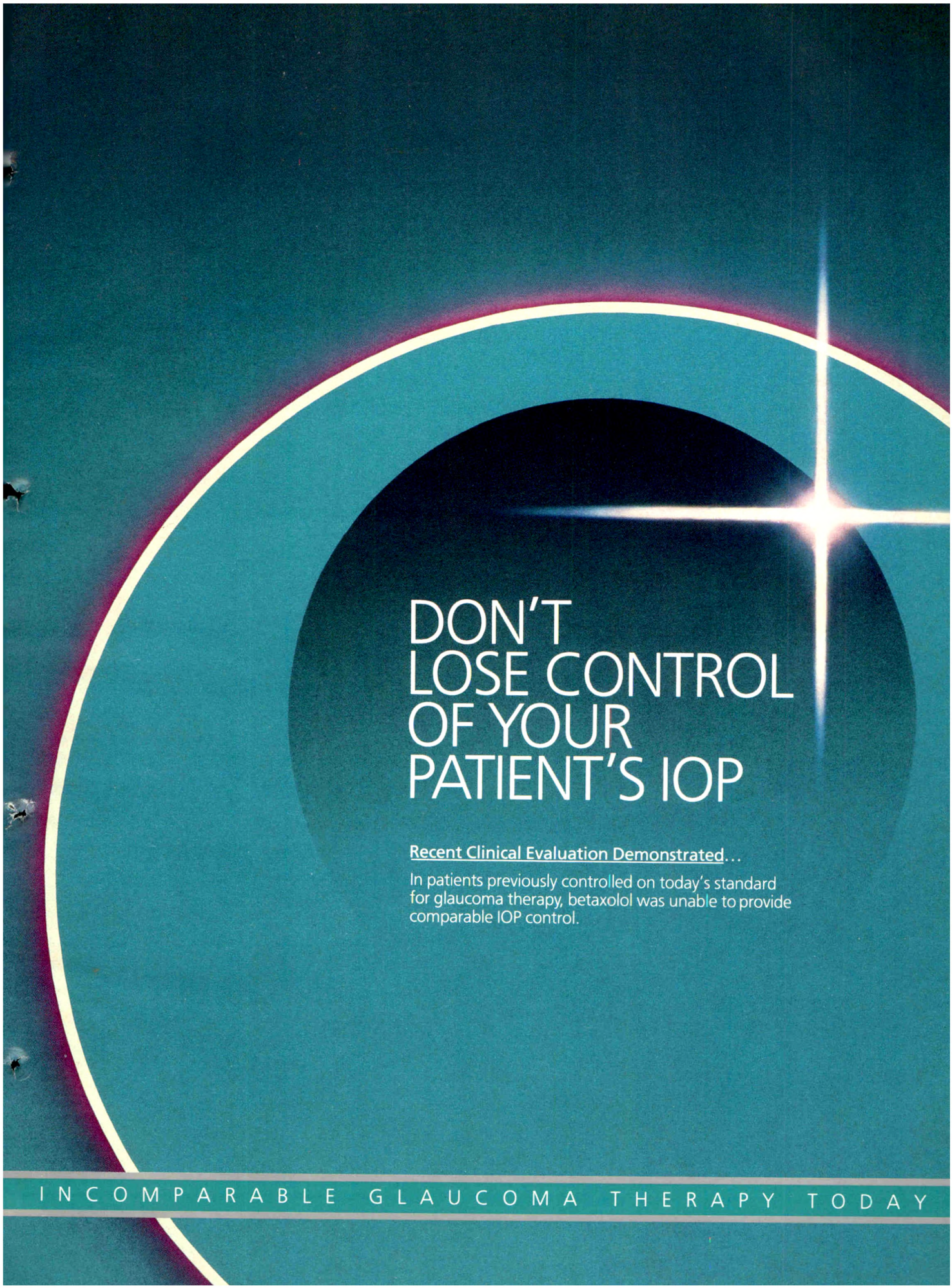
OPHTHALMOLOGY IN THE YEAR 2020

June 1–3, 1988

St. Francis Hotel, Union Square San Francisco, California

This course is intended to be one which looks to the future. While covering potential scientific advancements, the course will stress **practical developments** which are with us today and likely future developments of particular interest to practicing ophthalmologists. Areas of emphasis include cataract surgery, glaucoma, vitreo-retinal diseases, corneal and refractive surgery, ophthalmic pharmacology, pediatric ophthalmology, neuro-ophthalmology, and ophthalmic genetics. Prominent guest faculty join the faculty of UCSF Department of Ophthalmology to present this comprehensive and challenging assessment. The program also celebrates the dedication of the new *Beckman Vision Center* at UCSF.

For further information, please write or call Extended Program in Medical Education, Room 569-U, University of California School of Medicine, San Francisco, California 94143-0742, (415) 476-4251.

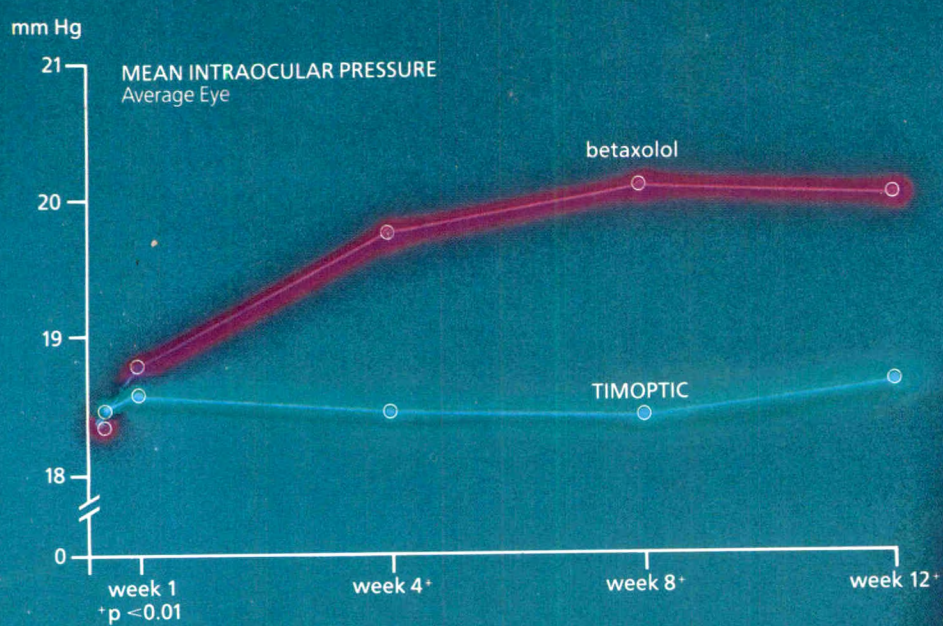

DON'T
LOSE CONTROL
OF YOUR
PATIENT'S IOP
Recent Clinical Evaluation Demonstrated...
In patients previously controlled on today's standard for glaucoma therapy, betaxolol was unable to provide comparable IOP control.
INCOMPARABLE GLAUCOMA THERAPY TODAY

DON'T LOSE CONTROL OF YOUR PATIENT'S IOP

In a multicenter study, recent clinical evaluation,[1,2] of 353 patients with a history of satisfactory IOP control and tolerability while on TIMOPTIC® (Timolol Maleate, MSD):

- Confirmed the benefits of maintaining therapy with TIMOPTIC for IOP control
- Demonstrated that TIMOPTIC surpassed Betoptic in maintaining IOP control

In patients previously controlled on TIMOPTIC, Betoptic was unable to maintain comparable IOP control:



At week 12, 97% of 149 patients on TIMOPTIC continued to be satisfactorily controlled.

At weeks 4, 8, and 12, significant increases in baseline IOP ($p \leq 0.01$) were seen in the patients treated with Betoptic.

[1]Data available upon request from Merck Sharp & Dohme, Professional Services Department, West Point, PA 19486.

[2]A total of 353 patients whose IOP was satisfactorily controlled with TIMOPTIC and in whom the drug was well tolerated were continued on TIMOPTIC 0.5% b.i.d. during a 2-week baseline period. Patients contributing data were then randomly assigned in a double-masked fashion in demographically similar groups to continue to receive either TIMOPTIC 0.5% b.i.d. (n = 149) or Betoptic 0.5% b.i.d. (n = 146). Following a baseline measurement, patients were evaluated for IOP after 1, 4, 8, and 12 weeks of therapy. In the average-eye approach, values from the right and left eye were averaged at each time point to obtain the values used in the analysis. In the worst-eye approach, the eye with the higher baseline IOP was followed throughout the course of the study.

As with the use of other antiglaucoma drugs, diminished responsiveness to TIMOPTIC after prolonged therapy has been reported in some patients. However, in one long-term study in which 96 patients have been followed for at least 3 years, no significant difference in mean IOP has been observed after initial stabilization.

TIMOPTIC is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; and hypersensitivity to any component of this product.

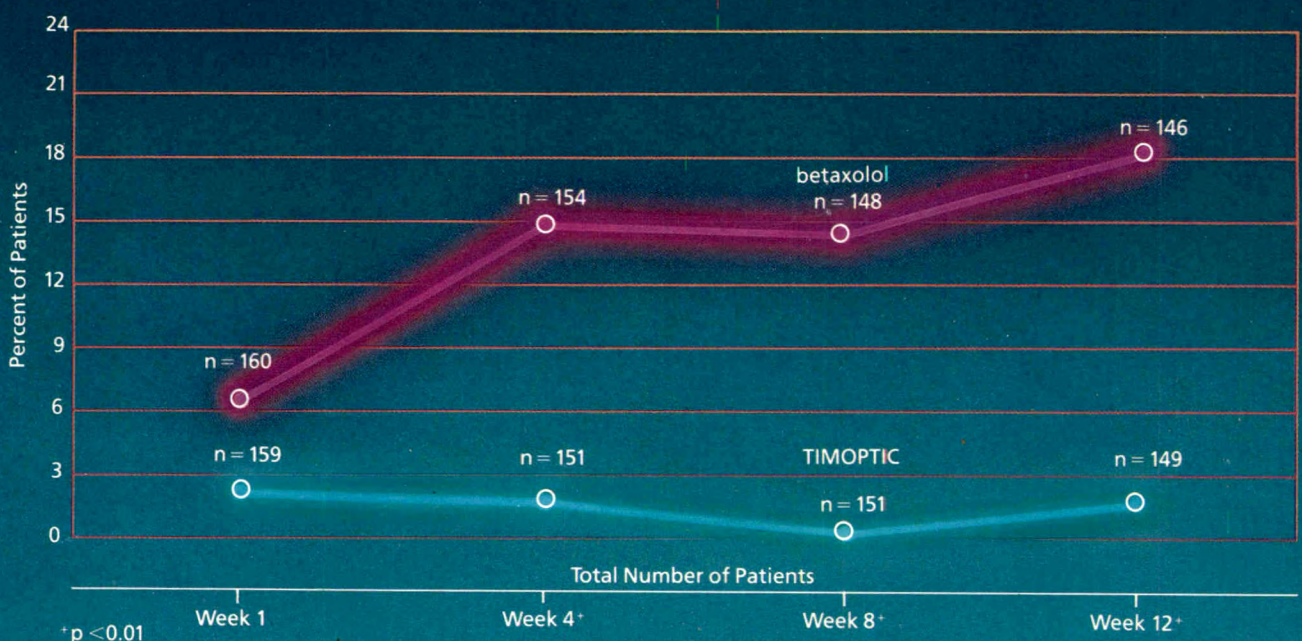
I N C O M P A R A B L E G L A

NOTE: Betoptic is the registered trademark of Alcon Laboratories, Inc. for betaxolol hydrochloride.

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PATIENTS EXHIBITING CHANGES IN INTRAOCULAR PRESSURE (FROM TREATED BASELINE) ≥ +5 mm Hg

Worst Eye



+p <0.01

Nearly 1 out of 5 patients treated with Betoptic showed an increase in IOP ≥ +5 mm Hg at week 12

For the majority of patients with chronic open-angle glaucoma or elevated IOP who are at sufficient risk to require therapy

TIMOPTIC®

(TIMOLOL MALEATE | MSD)

STERILE OPHTHALMIC SOLUTION

C O M A T H E R A P Y T O D A Y

Before prescribing TIMOPTIC, please see the Brief Summary of Prescribing Information on the following page.

TIMOPTIC®

(TIMOLOL MALEATE) MSD

STERILE OPHTHALMIC SOLUTION

How to start patients on TIMOPTIC:
Usual starting dosage: one drop 0.25% TIMOPTIC in the affected eye(s) twice a day.

How to transfer from another topical ophthalmic beta-adrenergic blocking agent to TIMOPTIC:

1. On the first day, after proper dosing, discontinue the topical agent being used.

2. On the second day, start treatment with one drop of 0.25% TIMOPTIC in the affected eye(s) b.i.d.

How to transfer from a single antiglaucoma agent (other than a topical ophthalmic beta-adrenergic blocking agent) to TIMOPTIC:

1. On the first day, continue with the agent already being used and add one drop 0.25% TIMOPTIC in the affected eye(s) b.i.d.

2. On the second day, discontinue the previously used agent and continue with TIMOPTIC in the affected eye(s) b.i.d.

How to transfer from several concomitantly administered antiglaucoma agents to TIMOPTIC:

1. If any agent is an ophthalmic beta-adrenergic blocker, discontinue before starting TIMOPTIC.

2. Continue the other agents being used, but add one drop of 0.25% TIMOPTIC to the affected eye(s) b.i.d.

3. On the following day, discontinue one of the other antiglaucoma agents.

4. The remaining antiglaucoma agents may be decreased or discontinued according to the patient's response to treatment.

If clinical response is not adequate:
Dosage may be increased (from the 0.25% solution) by changing to one drop 0.5% TIMOPTIC twice a day in the affected eye(s). Dosages above one drop of 0.5% TIMOPTIC twice a day generally have not been shown to produce further reduction of IOP. If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s).

In patients with a history of severe cardiac disease, signs of cardiac failure should be watched for and pulse rates should be checked.

CONTRAINDICATIONS: TIMOPTIC is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to any component of this product.

WARNINGS: As with other topically applied ophthalmic drugs, this drug may be absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death in association with cardiac failure, have been reported following administration of TIMOPTIC (see CONTRAINDICATIONS).

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, TIMOPTIC should be discontinued.

Obstructive Pulmonary Disease: PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (e.g., CHRONIC BRONCHITIS, EMPHYSEMA) OF MILD OR MODERATE SEVERITY, BRONCHOSPASTIC DISEASE OR HISTORY OF BRONCHOSPASTIC DISEASE (OTHER THAN BRONCHIAL ASTHMA OR HISTORY OF BRONCHIAL ASTHMA, IN WHICH 'TIMOPTIC' IS CONTRAINDICATED, see CONTRAINDICATIONS), SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS, INCLUDING 'TIMOPTIC'. However, if TIMOPTIC is necessary in such patients, then the drug should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution to patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

PRECAUTIONS: *General:* Patients who are receiving a beta-adrenergic blocking agent orally and TIMOPTIC should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Patients should not receive two topical ophthalmic beta-adrenergic blocking agents concurrently.

Because of potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with TIMOPTIC, alternative therapy should be considered.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. TIMOPTIC has little or no effect on the pupil. When TIMOPTIC is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone.

As with the use of other antiglaucoma drugs, diminished responsiveness to TIMOPTIC® (Timolol Maleate MSD) after prolonged therapy has been reported in some patients. However, in one long-term study in which 96 patients have been followed for at least three years, no significant difference in mean intraocular pressure has been observed after initial stabilization.

Drug Interactions: Although TIMOPTIC used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with TIMOPTIC and epinephrine has been reported occasionally.

Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Caution should be used in the coadministration of beta-adrenergic blocking agents, such as TIMOPTIC, and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Animal Studies: No adverse ocular effects were observed in rabbits and dogs administered TIMOPTIC topically in studies lasting one and two years respectively.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year oral study of timolol maleate in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human oral dose* (1 mg/kg/day). Similar differences were not observed in rats administered oral doses equivalent to 25 or 100 times the maximum recommended human oral dose. In a lifetime oral study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages up to 60 mg timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/mL). In Ames tests, the highest concentrations of timolol employed, 5000 or 10,000 μg/plate, were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human oral dose.

Pregnancy: Pregnancy Category C: Teratogenicity studies with timolol in mice and rabbits at doses up to 50 mg/kg/day (50 times the maximum recommended human oral dose) showed no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (1,000 times the maximum recommended human oral dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 100 times the maximum recommended human oral dose, in this case without apparent maternotoxicity. There are no adequate and well-controlled studies in pregnant women. TIMOPTIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established by adequate and well-controlled studies.

ADVERSE REACTIONS: TIMOPTIC Ophthalmic Solution is usually well tolerated. The following adverse reactions have been reported either in clinical trials of up to three years' duration prior to release in 1978 or since the drug has been marketed.

BODY AS A WHOLE: Headache, asthenia, chest pain. CARDIOVASCULAR: Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, palpitation, cardiac arrest. DIGESTIVE: Nausea, diarrhea. NERVOUS SYSTEM/PSYCHIATRIC: Dizziness, depression, increase in signs and symptoms of myasthenia gravis, paresthesia. SKIN: Hypersensitivity, including localized and generalized rash, urticaria. RESPIRATORY: Bronchospasm (predominantly in patients with preexisting bronchospastic disease), respiratory failure, dyspnea, nasal congestion. ENDOCRINE: Masked symptoms of hypoglycemia in insulin-dependent diabetics (see WARNINGS). SPECIAL SENSES: Signs and symptoms of ocular irritation, including conjunctivitis, blepharitis, keratitis, blepharoptosis, decreased corneal sensitivity, visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis.

Causal Relationship Unknown: The following adverse effects have been reported, and a causal relationship to therapy with TIMOPTIC has not been established: *Body as a Whole:* Fatigue; *Cardiovascular:* Hypertension, pulmonary edema, worsening of angina pectoris; *Digestive:* Dyspepsia, anorexia, dry mouth; *Nervous System/Psychiatric:* Behavioral changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence, and other psychic disturbances; *Skin:* Alopecia; *Special Senses:* Aphakic cystoid macular edema; *Urogenital:* Retroperitoneal fibrosis, impotence.

The following additional adverse effects have been reported in clinical experience with oral timolol maleate and may be considered potential effects of ophthalmic timolol maleate: *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Edema, worsening of arterial insufficiency, Raynaud's phenomenon, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting; *Hematologic:* Nonthrombocytopenic purpura; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating, cold hands and feet; *Musculoskeletal:* Arthralgia, claudication; *Nervous System/Psychiatric:* Vertigo, local weakness, decreased libido, nightmares, insomnia, diminished concentration; *Respiratory:* Rales, cough, bronchial obstruction; *Special Senses:* Tinnitus, dry eyes; *Urogenital:* Urination difficulties.

Potential Adverse Effects: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents and may be considered potential effects of ophthalmic timolol maleate: *Digestive:* Mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Agranulocytosis, thrombocytopenic purpura; *Nervous System:* Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Urogenital:* Peyronie's disease.

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis sicca, otitis, and sclerosing serositis attributed to the beta-adrenergic receptor blocking agent practolol. This syndrome has not been reported with timolol maleate.

HOW SUPPLIED: TIMOPTIC Ophthalmic Solution, 0.25% and TIMOPTIC Ophthalmic Solution, 0.5%. Both are available in 2.5-mL, 5-mL, 10-mL, and 15-mL plastic OCUMETER® ophthalmic dispensers with a controlled drop tip. **Also Available:** Preservative-free TIMOPTIC in OCUDOSE® (Dispenser) Sterile Ophthalmic Unit-Dose Dispenser (see separate Prescribing Information).

Storage: Protect from light. Store at room temperature.

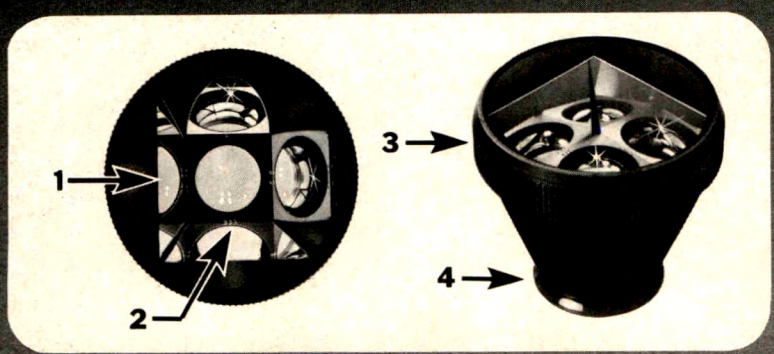
*The maximum recommended single oral dose is 30 mg of timolol. One drop of TIMOPTIC 0.5% contains about 1/150 of this dose, which is about 0.2 mg.

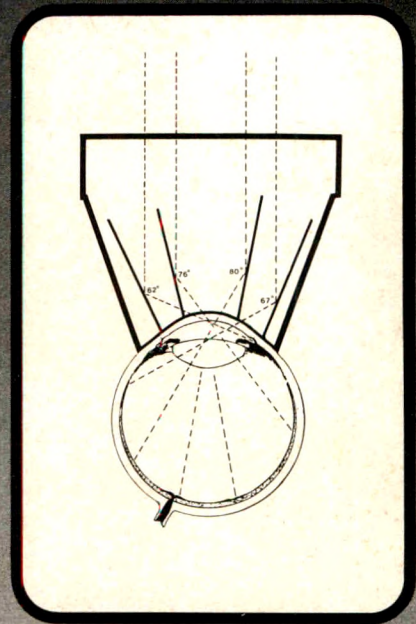
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For more detailed information, consult your MSD Representative and the Prescribing Information.
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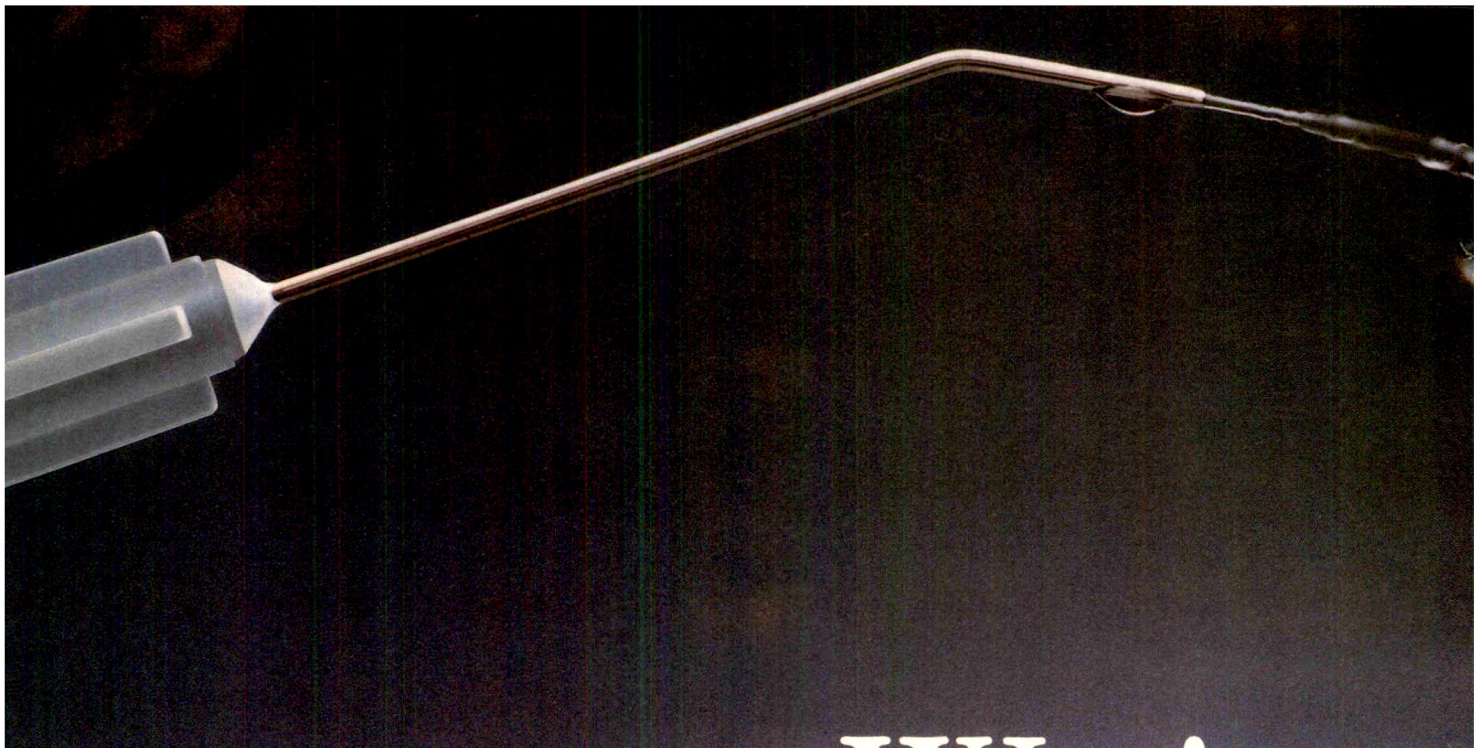
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- Central viewing area plus 4 mirrors (62°, 67°, 76°, 80°), the **fields** of which **overlap exactly** so that a lesion can be treated from the central area to the far periphery by simply rotating the lens.
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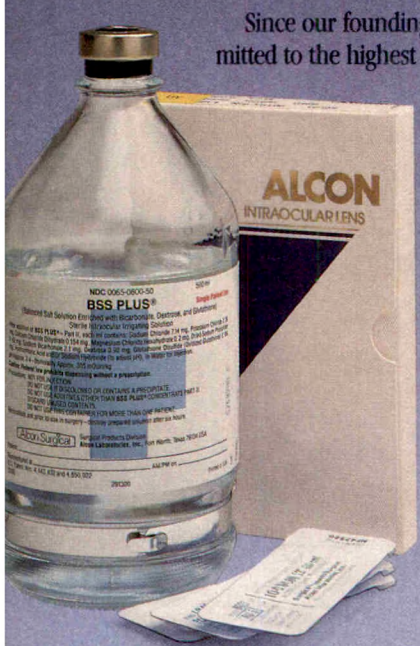
Designed by: John R. Karickhoff, M.D., Clinical Assistant Professor of Ophthalmology, Georgetown University, Washington, D.C.

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com-ple-ment n: something that completes, or makes perfect.



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—David Apple, M.D.
University of Utah, Center for Intraocular Lens Research

1 The funding for the Center for Intraocular Lens Research established at the University of Utah Health Sciences Center co from the private sector including awards from the ASCRS and donations by most of the lens manufacturers in the United States. These contributions are nonrestrictive. The Center is an independent research laboratory, and Dr. Apple has no proprietary interest in any lens company.



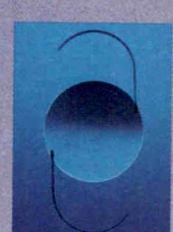
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1. Data on file at Alcon Laboratories Inc.

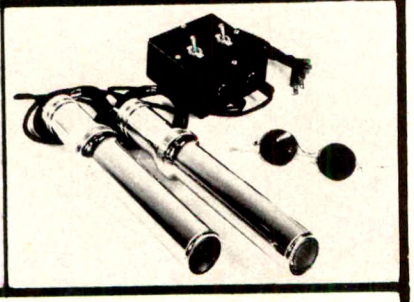
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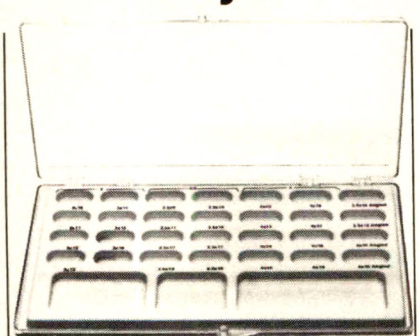
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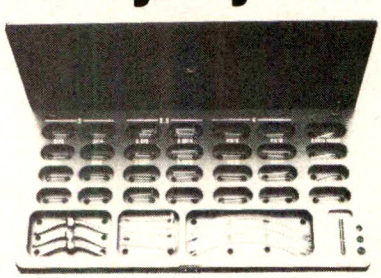
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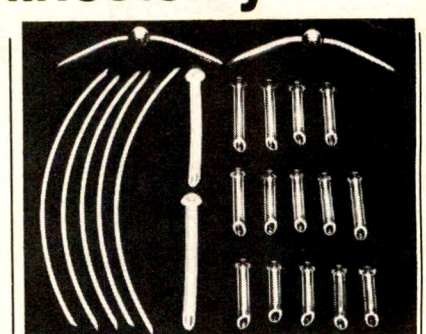
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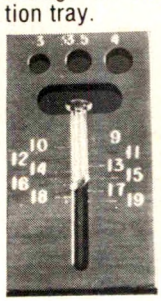
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*L.T. Jones M.D., Dacryocystorhinostomy, American Journal of Ophthalmology, Volume 59, No. 5, May, 1965.
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Predictors of Scleral Rupture and the Role of Vitrectomy in Severe Blunt Ocular Trauma

Stephen R. Russell, M.D., Karl R. Olsen, M.D., and James C. Folk, M.D.

We reviewed retrospectively 40 eyes that had received blunt trauma and had been explored for scleral rupture. Twenty-nine eyes had scleral rupture. Of these 29, ten had ruptures seen preoperatively. Nineteen had occult ruptures. The preoperative findings predictive of scleral rupture were a visual acuity of light perception or no light perception, an intraocular pressure of less than 10 mm Hg, hyphema, and chemosis. Of the 29 ruptures, 27 involved the superior hemisphere and 25 involved the anterior hemisphere of the globe. Ten of 29 eyes (34%) with scleral rupture and eight of 11 eyes (73%) without rupture achieved a final visual acuity of 5/200 or better over an average follow-up period of 6.7 months. Factors prognostic of ambulatory vision for eyes with ruptured and intact globes included an initial visual acuity of 5/200 or better, absence of scleral rupture, and a rupture length of less than 11 mm in eyes with ruptures. The vitrectomized eyes also had a better result, suggesting that early pars plana vitrectomy is of benefit in selected rupture cases.

© American Journal of Ophthalmology 105:253–257, March, 1988

Maternal Corneal Thickness During Pregnancy

Robert N. Weinreb, M.D., Arthur Lu, M.D., and Charles Beeson, M.D.

We measured central corneal thickness in 89 pregnant women. It was increased 16 μm ($P = .01$) compared to the control eyes of 18 nongravid and 17 postpartum women. There was no significant difference ($P = .79$) in corneal thickness between the nongravid and postpartum groups. When comparing subjects by week of gestation, there was no trend over time in corneal thickness (analysis by linear regression). Intraocular pressure was lowered during pregnancy, but it did not correlate with corneal thickness for either the pregnant or nonpregnant group.

© American Journal of Ophthalmology 105:258–260, March, 1988

Enlargement of the Blind Spot Caused by Papilledema

James J. Corbett, M.D., Daniel M. Jacobson, M.D., Richard C. Mauer, M.D., and H. Stanley Thompson, M.D.

Blind spot enlargement in papilledema has been attributed to either mechanical disruption of the integrity of the peripapillary percipient elements by the swollen optic disk or to the Stiles-Crawford effect. We investigated the possibility that blind spot enlargement in papilledema is caused, at least in part, by a refractive scotoma due to peripapillary hyperopia. We reduced the enlarged blind spot in a patient with focal peripapillary hyperopia, without papilledema, to near normal size by using progressively stronger plus lenses. Similarly, with the addition of plus sphere, we reduced the size of the blind spot in five of six patients with papilledema, but in none of our normal subjects.

© American Journal of Ophthalmology 105:261–265, March, 1988

Recombinant Tissue Plasminogen Activator to Lyse Experimentally Induced Retinal Arterial Thrombi

Andrew K. Vine, M.D., Paul T. Maguire, M.D., Csaba Martonyi, and Marilyn C. Kincaid, M.D.

We evaluated the efficacy of intravenously administered recombinant tissue plasminogen activator to lyse laser-induced arterial thrombi in the stroke-prone, spontaneously hypertensive rat model. The arterial thrombi were confirmed histologically, and assessed by color photographs and fluorescein angiography before and after intravenous tissue plasminogen activator or saline therapy. Experimental animals received tissue plasminogen activator (1 mg/kg of body weight) given intravenously over one hour, and control animals received similar volumes of normal saline. Tissue plasminogen activator was effective in lysing experimental retinal arterial thrombi.

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VOLUME 105 NUMBER 3 MARCH, 1988

Aldose Reductase Inhibitor (CT-112) Eyedrops for Diabetic Corneal Epitheliopathy

Yuichi Ohashi, M.D., Mamoru Matsuda, M.D., Hisashi Hosotani, M.D., Yasuo Tano, M.D., Ichiro Ishimoto, M.D., Masakatsu Fukuda, M.D., and Reizo Manabe, M.D.

We treated two diabetic patients with corneal epithelial disorder that resisted conventional medical therapy with topical CT-112 (5-[3-ethoxy-4-pentyloxyphenyl]-2,4-thiazolidinedione), a newly synthesized aldose reductase inhibitor. One patient had developed recurrent corneal erosion after vitrectomy and the other had spontaneously developed superficial punctate keratopathy. The corneal lesion in each patient responded to topical CT-112 in two to four weeks and was almost cleared within two months. A similar corneal lesion reccurred in both patients soon after CT-112 was discontinued, but it disappeared again when the drug was resumed.

MANY PROBLEMS involving the corneal epithelium have been reported in patients with diabetes mellitus, particularly after intraocular surgery.[1-3] While the development of vitreous surgery has enabled us to treat proliferative diabetic retinopathy, it has also introduced a new spectrum of corneal disorders. Most corneal complications are caused by superficial punctate keratopathy,[4] recurrent corneal erosion,[3] and persistent epithelial defect or trophic ulceration.[5] These epithelial abnormalities can persist over weeks and are often difficult to treat.

Although the pathogenetic mechanism for diabetic corneal epitheliopathy is unclear, it has been postulated that aldose reductase, the first enzyme of the sorbitol pathway, might be involved in the pathogenesis of such abnormalities as it is in the diabetic complications of other tissues.[6-8] Immunohistochemical studies have shown that aldose reductase is present in the basal layer of corneal epithelium.[9,10] Experimental studies have also shown that aldose reductase inhibitors are effective in promoting corneal reepithelialization in streptozotocin-induced diabetic[11] and galactosemic rats.[12]

Herein we describe two patients with diabetic corneal epitheliopathy who showed a dramatic response to treatment with topical CT-112 (5-[3-ethoxy-4-pentyloxyphenyl]-2,4-thiazolidinedione), a newly synthesized aldose reductase inhibitor.[13]

Case Reports

Case 1

This 67-year-old man, with a 30-year history of diabetes mellitus, had proliferative diabetic retinopathy in both eyes. Visual acuity was R.E.: hand motions and L.E.: 2/200. On Dec. 15, 1984, he underwent pars plana vitrectomy coupled with lensectomy in the right eye. The operation was uneventful, except that the surgeon had to abrade the corneal epithelium during surgery to restore adequate visualization of the fundus.

Postoperatively, the retina was reattached and visual acuity had improved to R.E.: 5/100. The patient was given 0.1% dexamethasone and 0.3% tobramycin four times a day. The corneal epithelial defect healed in three days. On postoperative day 7, the intraocular pressure was slightly increased to 23 mm Hg, and 0.5% timolol maleate twice a day was added to

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the regimen. Thereafter, the intraocular pressure remained below 20 mm Hg. Slit-lamp examination one week after the operation showed that the central corneal epithelium was redundantly attached to the underlying stroma, and there was a moderate degree of stromal edema. These corneal findings remained unchanged for one month.

On Jan. 20, 1985, the patient suddenly suffered severe pain in the right eye on awakening. Slit-lamp examination disclosed a large epithelial erosion in the central cornea. The corneal epithelium around the defect margin was noted to be loosely attached to the underlying stroma (Fig. 1, top). There was slight folding of Descemet's membrane and stromal edema. The anterior chamber reaction was minimal. Intraocular pressure was normal by palpation.

The patient's right eye was patched and erythromycin ointment was used as a lubricant. Although the epithelial defect healed in four days, the regenerated epithelium was again found to be poorly attached to the underlying stroma. Because recurrent corneal erosion resulted from the damage in the basement membrane caused by the intraoperative epithelial abrasion, the topical use of aldose reductase inhibitor was suggested.

After obtaining informed consent, 0.5% CT-112 dissolved in an acetate buffer solution was applied to the right eye four times a day. CT-112 is a noncompetitive inhibitor and its 50% inhibition concentrations for aldose reductase are similar to those of sorbinil.[14] Previous experiments have demonstrated that topical instillation of CT-112 is effective in preventing polyol accumulation in the corneal epithelium and promoting reepithelialization in galactosemic rats (unpublished data).

Ten days after the initiation of topical CT-112, the redundancy of the corneal epithelium disappeared almost entirely (Fig. 1, middle). The treatment was continued for two additional weeks, during which time the condition of the right cornea remained stable.

On Feb. 25, 1985, however, the patient again complained of pain in the right eye. He had discontinued the use of topical CT-112 one week previously because of mild irritation upon instillation. On slit-lamp examination, a large corneal epithelial bulla had formed at the site of the original epithelial defect (Fig. 1, bottom). The bulla developed into an epithelial defect the next day. The patient's right eye was patched and the treatment with topical CT-112

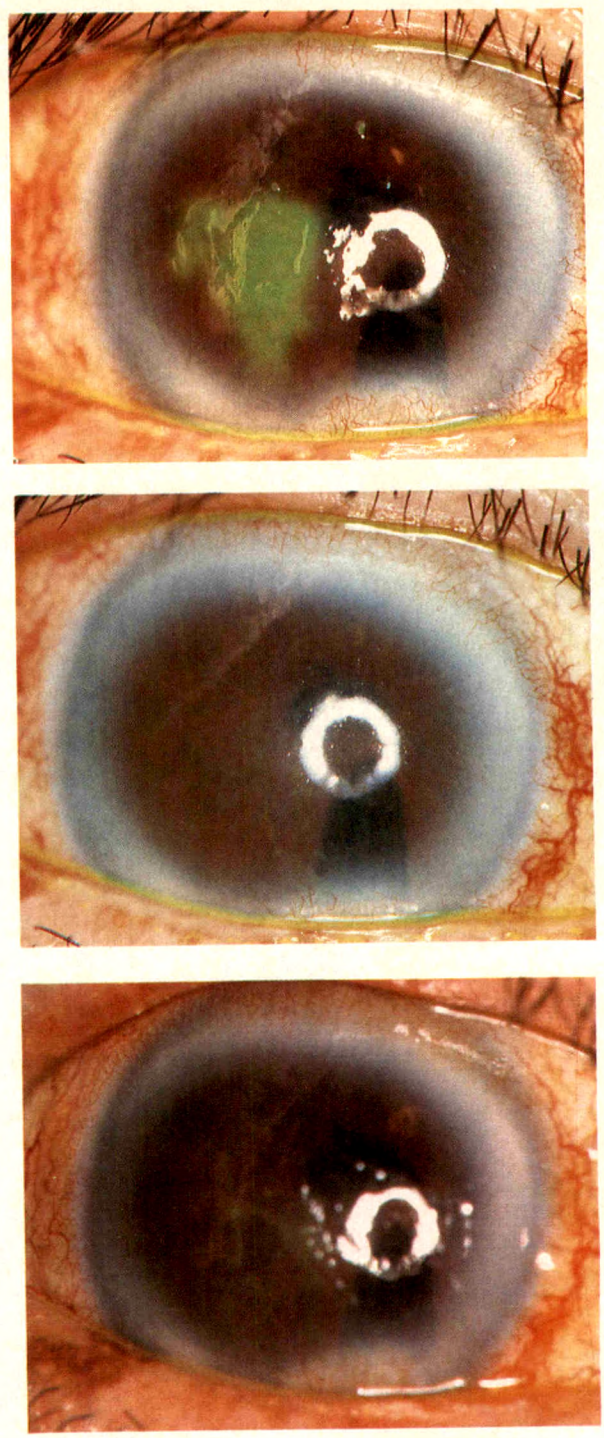


Fig. 1 (Ohashi and associates). Top, Case 1, right eye. Before topical CT-112 therapy. Note large corneal erosion. Middle, Ten days after initiating topical CT-112. The corneal epithelium appeared firmly attached. Bottom, One week after discontinuing topical CT-112. A large corneal epithelial bulla was formed at the almost same location.

was resumed. The epithelial defect healed again within four days. The defect has not recurred for almost two years with continuous use of topical CT-112.

Case 2

This 56-year-old man, with an 18-year history of adult-onset diabetes mellitus, was seen at the Diabetic Retinopathy Service at our institution. In May 1985, when preproliferative diabetic retinopathy developed, he noticed blurred vision in his left eye. Visual acuity was R.E.: 20/20 and L.E.: 15/20. On slit-lamp examination, multiple punctate erosions were found over the surface of the left cornea. The use of ocular lubricants for the next six months was unsuccessful.

In October 1985 the patient was referred to the Corneal Service because of superficial punctate keratopathy of unknown origin. Slit-lamp examination disclosed a severe superficial punctate keratopathy in the left eye. No abnormalities were found in the left eyelid or on the conjunctiva. The tear meniscus was of normal height. The corneal sensitivity was reduced, as demonstrated by application of a wisp of cotton. No significant pathogens were isolated from the eyelid margin or from the conjunctiva. The cause of this particular superficial punctate keratopathy was not determined. Thereafter, he was generally treated with ocular lubricants and occasionally with eye patching when the corneal lesion was exacerbated.

On April 22, 1986, the patient was again referred to the Corneal Service. Slit-lamp examination disclosed a severe superficial punctate keratopathy over the entire surface of the left cornea (Fig. 2, top left). There were no abnormalities of the eyelid or the conjunctiva. The tear meniscus was of normal height. Photokeratoscopy demonstrated a marked irregularity of the corneal surface (Fig. 2, top right). The corneal sensitivity, as measured by the Cochet-Bonnet esthesiometer, was reduced to 15 mm in the left eye. Visual acuity had deteriorated to 20/200.

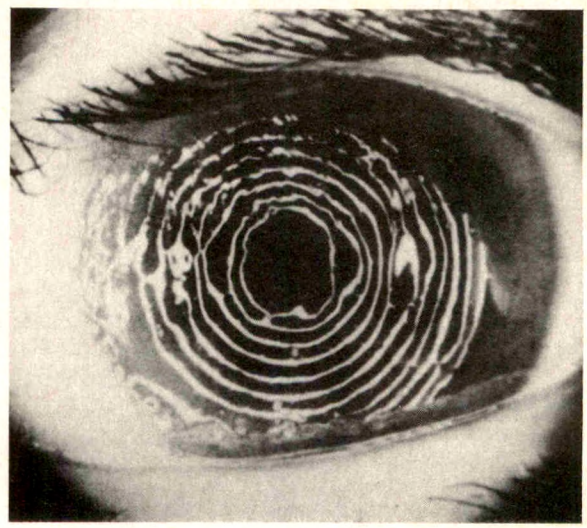
This condition did not respond to topical lubricant applied four times a day for two weeks. We suspected persistent superficial punctate keratopathy, probably resulting from reduced corneal sensitivity. After obtaining informed consent, topical CT-112 was applied to the cornea four times a day, with concomitant use of a lubricant. Four weeks later, the superficial punctate keratopathy was markedly reduced. After another four weeks, the corneal epithelial changes had almost completely disappeared (Fig. 2, middle left). This improvement was clearly shown by photokeratoscopy (Fig. 2, middle right). Corneal sensitivity returned to normal and visual acuity improved to L.E. 15/20.

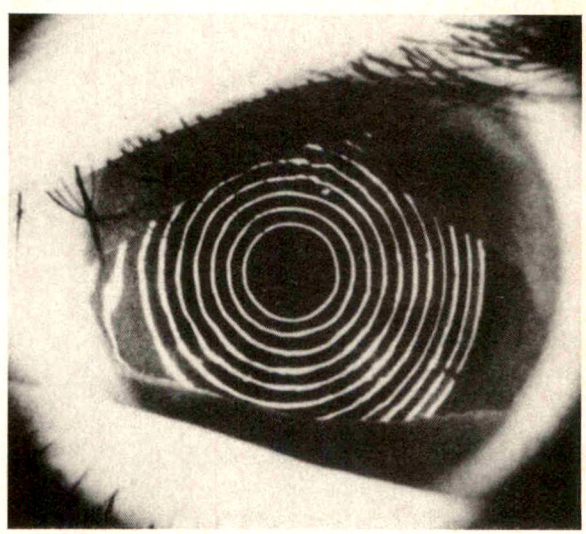
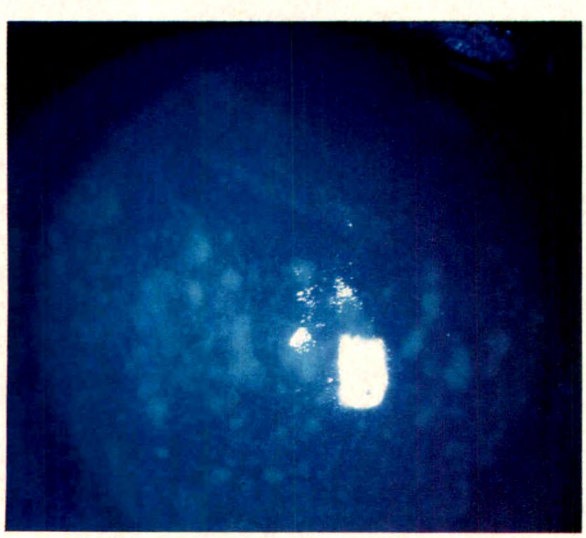
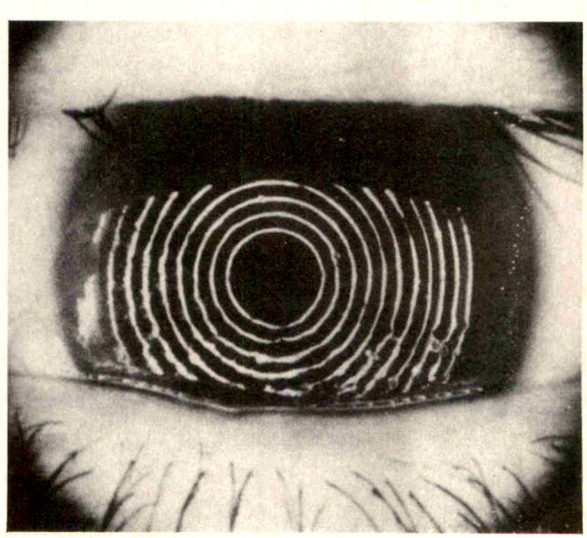
Three months later, the superficial punctate keratopathy had cleared and treatment was discontinued. However, two weeks later, a moderate degree of superficial punctate keratopathy again developed in the left cornea (Fig. 2, bottom left), as seen on photokeratoscopy (Fig. 2, bottom right). Visual acuity had decreased to L.E.: 20/200. Topical CT-112 four times a day was reinstituted and, over the course of four weeks, the superficial punctate keratopathy gradually healed. Visual acuity improved to 20/30. This patient has since remained asymptomatic with continuous use of CT-112.

Discussion

Over the past decade the corneal epithelial disorders seen in diabetic patients after intraocular surgery have become a serious clinical problem. Previous experimental, as well as clinical, surveys have conclusively shown that the corneal epithelium in diabetics is at a greater risk from undue stress as compared to that in normal subjects.[1-3,15,16] A survey by Schultz and associates[4] showed that many diabetic patients spontaneously display a varied degree of superficial punctate erosions on the cornea. Similarly, our Patient 1 developed recurrent corneal erosion after pars plana vitrectomy, possibly resulting from damage to the epithelial basement membrane caused by abrasion of the epithelium during surgery. In Patient 2, superficial punctate keratopathy occurred without any stress to the cornea. It was probably caused by impairment of the corneal nerve, which was a manifestation of the diabetic neuropathy.[17,18] Neither patient responded favorably to conventional medical therapy.

Previous studies have suggested that aldose reductase may be involved in the development of diabetic corneal epithelial abnormalities. First, immunohistochemical studies have shown the existence of aldose reductase in the corneal epithelium of animals and humans.[9,10] Second, it has been demonstrated that corneal reepithelialization is significantly increased in diabetic[11] and galactosemic rats[12] treated with

an aldose reductase inhibitor. Furthermore, Foulks and associates[3] detected increased amounts of sorbitol in the corneal epithelium from diabetic patients than that found in normal controls. This evidence led us to consider the use of topical aldose reductase inhibitor in the management of the epithelial abnormalities seen in both of our patients.

To the best of our knowledge, topical aldose reductase inhibitor (sorbinil) was first used by Cogan and associates.[7] He treated one case of intractable corneal ulceration, which responded dramatically to the topical sorbinil. Consistent with his result, topical aldose reductase inhibitor (CT-112) was found to be effective in treating both patients described herein. In our patients, the response to CT-112 occurred within a few weeks, and was immediately followed by resolution of the epithelial abnormalities. After discontinuation of topical CT-112, however, the characteristic epithelial lesions recurred in both patients. The lesions resolved again with readministration of topical aldose reductase inhibitor. These observations suggest that epithelial abnormalities in diabetic patients might be at least partly caused by abnormal activation of the sorbitol pathway. However, the exact mechanisms by which aldose reductase triggers such abnormalities remain unknown.

Our observations indicate that topical aldose reductase inhibitor (CT-112) may be useful in treating diabetic corneal epitheliopathy. It has been demonstrated, in studies using diabetic rats, that topical CT-112 was found to be effective in preventing accumulation of sorbitol in the corneal epithelium[13] and in reducing the morphologic abnormalities of the corneal endothelium.[19] Our preliminary clinical trial of topical aldose reductase inhibitor (CT-112) has been successful in patients with diabetic corneal epitheliopathy.[20] To explore the questions of safety, risks, and benefits, particularly on a long-term basis, we are currently conducting a randomized, controlled clinical study of CT-112.

Acknowledgment

Senju Pharmaceutical Co., Ltd., Osaka, Japan, supplied the CT-112 eyedrops.

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Fig. 2 (Ohashi and associates). Case 2, left eye. Top left, Before topical CT-112 therapy. Multiple punctate erosions were found on the entire surface of the cornea. Top right, Photokeratoscopy showed a high degree of surface irregularity. Middle left, Eight weeks after initiating topical CT-112. Punctate keratopathy was almost cleared. Middle right, The photokeratoscopic pattern was almost normal. Bottom left, Two weeks after discontinuing topical CT-112. Multiple punctate erosions recurred on the entire surface of the cornea. Bottom right, Photokeratoscopy showed a moderate degree of surface irregularity.

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OPHTHALMIC MINIATURE

When I came to,
the air I drifted in trembled around me
to a vast distance with sighs
—not from any great grief, but disturbed
by countless forms drifting as I did,
wavery albumen bodies
each burdened with an eye. Poor spirits!
How tentative and slack our search
along the dun shore whose perpetual hiss
breaks softly, and breaks again,
on endless broken shells! Stare as we will
with our red protein eyes, how few we discover
that are whole—a shell here and there
among so many—to slip into and grow blank!
Once more all faded.

Thomas Kinsella, "Notes From the Land of the Dead"
POEMS 1956–1973
Winston-Salem, North Carolina,
Wake Forest University Press, 1979, p. 131

Fortified Antibiotic Ointment in Bacterial Keratitis

Robert A. Hyndiuk, M.D., Daniel N. Skorich, M.D., Starkey D. Davis, M.D., Larrie D. Sarff, M.D., Kathy Divine, M.S., and Eileen Burd, M.S.

We conducted experiments to determine the effectiveness of fortified antibiotic ointment in the treatment of *Pseudomonas* keratitis in rabbits. We evaluated gentamicin ointment (3, 10, 20, and 40 mg/g), gentamicin solution (3 and 10 mg/ml), and placebo, each given every 30 minutes. We also examined the effectiveness of fortified ointment given in extended treatment intervals. In short-term trials, commercial-strength gentamicin solution (3 mg/ml) was therapeutically superior ($P < .001$) to commercial-strength gentamicin ointment (3 mg/g) in reducing corneal bacterial colony counts. No significant difference in antimicrobial effect was noted between fortified gentamicin ointment and fortified gentamicin solution at 30-minute treatment intervals. Fortified gentamicin ointment reduced colony counts even at extended treatment intervals of up to four hours in a severe keratitis model.

ANTIBIOTIC SOLUTIONS have been shown to be effective in the treatment of experimental bacterial keratitis.[1-6] Increasing the concentration of antibiotic solution enhances the antimicrobial efficacy.[5] Few studies, however, have compared the effectiveness of antibiotic ointments to solutions in the treatment of experimental bacterial keratitis. In a previous study using an experimental staphylococcal keratitis model, commercial-strength bacitracin ointment 500 units/g and commercial-strength erythromycin ointment were ineffective in reducing bacterial corneal colony counts.[6] In general, ointments may be less effective than solutions either because of theoretical binding of drug in the ointment vehicle[7,8] or because of the low concentrations of antibiotic available in all presently available commercial ophthalmic antibiotic ointment preparations.[9,10] In a questionnaire survey, Fraunfelder and Hanna[11] found that only 37% of ophthalmologists routinely used ointments in the treatment of corneal ulcer.

This study was designed to determine whether an ointment is an appropriate vehicle for the antibiotic therapy of bacterial keratitis, that is, whether antibiotics in ointments effectively reduce bacterial colony counts when compared to solutions. The effectiveness of various concentrations and frequency of administration of antibiotic ointment (gentamicin) was evaluated in the treatment of *Pseudomonas* keratitis in rabbits and compared to commercial-strength and fortified antibiotic solutions applied at frequent intervals.

Material and Methods

The method for producing *Pseudomonas* keratitis has been previously described and evaluated in detail.[1,12,13] A 25-gauge needle was used to make a 3-mm scratch in the corneas of New Zealand white rabbits. The scratched eyes were then infected with two drops of an undiluted overnight broth culture of *P. aeruginosa* strain 107 (previously calculated to contain approximately 5×10^8 organisms per milliliter). Another group of rabbits were injected intracorneally with about 20 viable *P. aeruginosa* strain 107 in a volume of 20 μl, with a microsyringe and a 30-gauge needle, producing a severe keratitis.[14] Treatment was begun after 24 hours of incubation, when all animals clinically had keratitis, and was continued for six and 24 hours. The animals were killed and a 6-mm corneal button

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TABLE 1
SIX- AND 24-HOUR TREATMENT OF EXPERIMENTAL *PSEUDOMONAS* KERATITIS (SCRATCH MODEL)

GROUP	TREATMENT	STRENGTH	DOSE INTERVAL (MIN)	NO. OF EYES	COLONY COUNTS (MEAN ± S.D. IN LOG UNITS) SIX-HOUR*	24-HOUR†
1	Placebo	0.15 M	30	6	6.19 ± 0.39	5.16 ± 0.91
2	Gentamicin ointment	3 mg/g	30	6	3.95 ± 0.82	0.35 ± 0.65
3	Gentamicin solution	3 mg/ml	30	6	1.89 ± 0.76	1.05 ± 0.82

*1 vs 2 or 3, $P < .001$; 2 vs 3, $P < .001$.
†1 vs 2 or 3, $P < .001$; 2 vs 3, $P = .1$.

was trephined, rinsed with saline, and ground in 0.9 ml of Mueller-Hinton broth. One-tenth-milliliter aliquots of serial dilutions of the cornea in broth were inoculated on agar plates. The plates were incubated overnight and the numbers of colonies were counted.

Topical therapy consisted of either two drops of solution or a ½-inch strip of ointment placed in the cul-de-sac. Specially formulated fortified gentamicin sulfate ointment (10, 20, and 40 mg/g) was obtained. The ointment was packaged in the customary commercial-sized tube. All other antibiotics were obtained from our hospital pharmacy.

Results were evaluated statistically by analysis of variance and the method of least significant differences.[15] Numbers of bacteria in the cornea are presented as arithmetic means and standard deviations of common logarithms (base 10). The arithmetic mean of common logarithms is equivalent to the geometric mean. The method of calculation, which dampens the effect of single extreme values, is commonly used in the analysis of numbers of microorganisms.[13]

Subculture contamination by adherent surface ointment was a potential source of error. To determine any possible carryover of antibiotic into the subcultures, rabbit eyes were scratched with a 25-gauge needle and then treated immediately as follows: (a) Group 1 received two drops of saline per eye, (b) Group 2 received two drops of 40-mg/g gentamicin solution, and (c) Group 3 received one application of 40-mg/g gentamicin ointment. The animals were killed 30 minutes after treatment. The corneas were removed, rinsed with saline, placed into grinders, ground in 0.9 ml of Mueller-Hinton broth into which had been added 0.1 ml of a 10^{-4} dilution of an overnight broth culture of *Pseudomonas* 107, and plated. Each grinder contained approximately 1.38×10^5 organisms per milliliter.

Results

The commercial-strength gentamicin ointment and solution, each applied every 30 minutes, reduced colony counts significantly compared to the control (Table 1). However, early in the treatment course (six-hour trial), commercial-strength gentamicin solution was superior to commercial-strength gentamicin ointment in reducing corneal bacterial colony counts ($P < .001$) when the ointment and solution were given every 30 minutes. After 24 hours of treatment there was no significant difference between the ointment- or the solution-treated groups.

No significant therapeutic difference ($P = .22$) was observed between the fortified gentamicin solution and the fortified gentamicin ointments when each was given every 30 minutes (Table 2). Ointments continued to reduce colony counts over the course of a 24-hour trial.

In the antibiotic carryover experiments, no carryover of antibiotic was detected (Table 3).

In a comparison of topical fortified gentamicin ointment given in variable treatment intervals to placebo, gentamicin ointment 20 mg/g reduced colony counts, even when given at up to six-hour intervals (Table 4).

TABLE 2
SIX- AND 24-HOUR TREATMENT OF EXPERIMENTAL *PSEUDOMONAS* KERATITIS (SCRATCH MODEL)

GROUP	TREATMENT	STRENGTH	DOSE INTERVAL (MIN)	NO. OF EYES	6-HOUR COLONY COUNTS* (MEAN ± S.D.)	NO. OF EYES	24-HOUR COLONY COUNTS† (MEAN ± S.D.)
1	Placebo	0.15 M	30	6	6.54 ± 0.37	12	4.79 ± 1.37
2	Gentamicin solution	10 mg/ml	30	5	1.57 ± 1.23	—	—
3	Gentamicin ointment	10 mg/g	30	5	2.67 ± 0.73	12	0.30 ± 0.55
4	Gentamicin ointment	20 mg/g	30	6	1.38 ± 1.23	12	0.22 ± 0.55
5	Gentamicin ointment	40 mg/g	30	6	1.50 ± 1.26	12	0.11 ± 0.38

*1 vs 2, 3, 4, or 5, $P < .001$; 2 vs 3, 4, or 5, $P > .1$.
†1 vs 3, 4, or 5, $P < .001$.

In the six-hour trial, the effectiveness of fortified ointment in a model of severe keratitis (intracorneal injection) was moderately variable within groups, with respect to standard deviations (Table 5). This pattern was seen in both the solution- and the ointment-treated groups. As intrastromal injection produces severe stromal keratitis of variable depth, the variation in colony counts within groups probably reflects incomplete penetration of the drug to all involved depths within the six-hour time frame. After 24 hours, colony counts were markedly reduced in all groups, as was variability within groups, indicating better penetration of the drug.

Discussion

Ointments, as vehicles for ocular drug delivery, may have advantages over solutions.[16-19]

TABLE 3
CARRYOVER OF ANTIBIOTIC OINTMENT IN BIOASSAY SUBCULTURES

GROUP	TREATMENT	NO. OF EYES	COLONY COUNTS* (MEAN ± S.D.)
1	Saline	9	4.75 ± 0.09
2	Gentamicin solution 40 mg/ml	8	4.66 ± 0.28
3	Gentamicin ointment 40 mg/g	8	4.71 ± 0.91

*1 vs 2 or 3, $P = .36$; 2 vs 3, $P = .59$.

Theoretically, a drug in an ointment vehicle should provide increased duration of action for several reasons: (1) less dilution of medication via the tear film, (2) sustained release of medication, and (3) prolonged ocular contact time. Certain lipid-soluble drugs, such as tetracycline and chloramphenicol, penetrate the cornea and aqueous humor more efficiently in an ointment vehicle when applied topically. However, of major clinical concern is the bioavailability of other drugs contained in an ointment vehicle.[7,8]

Our results showed that despite potential theoretical disadvantages, ointments were useful vehicles for antibiotic drug delivery and had the potential for a significant antimicrobial therapeutic effect. When concentrations of the antibiotic in the ointment were increased, the fortified gentamicin ointment was as effective as the fortified gentamicin solution at 30-minute dose intervals in both the shorter-term and long-term therapy trials. In addition, and of possibly greater clinical significance, the use of fortified gentamicin ointment allows one to extend the treatment interval (up to every four hours in the severe keratitis model), and still achieve significant microbial killing.

Factors affecting drug release in ointment have been reviewed by Riegelman.[19] As the solubility of most drugs in common ointments is low, the drug is present as microcrystals dispersed throughout the ointment. Only those crystals present at the tear-ointment interface are potentially available for tear solubilization, with the rest pharmacologically bound and not bioavailable. Since drugs must be in solution to be absorbed, it follows that whatever factors affect the dynamics of the tear-ointment inter-

TABLE 4
SIX-HOUR TREATMENT OF EXPERIMENTAL *PSEUDOMONAS* KERATITIS
(SCRATCH MODEL)

GROUP	TREATMENT	STRENGTH	DOSE INTERVAL	NO. OF EYES	COLONY COUNTS* (MEAN ± S.D.)
1	Placebo	0.15 M	30 min	6	5.62 ± 1.00
2	Gentamicin solution	10 mg/ml	30 min	6	2.03 ± 0.65
3	Gentamicin ointment	20 mg/g	30 min	5	1.97 ± 1.27
4	Gentamicin ointment	20 mg/g	Every 1 hour	5	2.05 ± 0.31
5	Gentamicin ointment	20 mg/g	Every 2 hours	6	2.08 ± 1.88
6	Gentamicin ointment	20 mg/g	Every 6 hours	6	3.65 ± 2.26

*1 vs 2, 3, 4, or 5, $P \leq .002$; 1 vs 6, $P = .1$; 2 vs 3, 4, or 5, $P \geq .93$; 2 vs 6, $P = .12$; 3 vs 4 or 5, $P \geq .90$; 3 vs 6, $P = .17$; 4 vs 5, $P = .96$; 4 vs 6, $P = .15$; 5 vs 6, $P = .22$.

face will also influence the amount of clinically available drug.

Most modern ophthalmic ointments consist of a mixture of white petrolatum and mineral oil, with or without lanolin. The vehicle is formulated to melt at body temperature, yet remain semisolid at room temperature. The importance of the vehicle in the ocular penetration of a drug cannot be underestimated.[8,16-18] The factors affecting the drug-vehicle-tear interaction are not completely understood, but may include concentration of the drug, solubility of the drug, characteristics of individual vehicles, tear film factors, presence of eyelid disease, presence of systemic disease, and interactions between simultaneously applied drugs.

The mechanism for the improved effectiveness of the fortified ointment, as compared to commercial-strength ointment, is probably related to the increased concentration of antibiotic in the ointment. If the drug is present as microcrystals dispersed throughout the ointment vehicle, it seems logical that increasing the concentration of the drug would increase the number of microcrystals available for solubilization within the tears and, therefore, improve the ointment's effectiveness. The mecha-

TABLE 5
SIX- AND 24-HOUR TREATMENT OF SEVERE EXPERIMENTAL *PSEUDOMONAS* KERATITIS
(INTRASTROMAL INJECTION MODEL)

GROUP	TREATMENT	STRENGTH	DOSE INTERVAL	NO. OF EYES	6-HOUR COLONY COUNTS* (MEAN ± S.D.)	NO. OF EYES	24-HOUR COLONY COUNTS† (MEAN ± S.D.)
1	Placebo	0.15 M	30 min	6	7.17 ± 0.20	6	6.78 ± 0.27
2	Gentamicin solution	10 mg/ml	30 min	6	3.17 ± 2.95	6	2.01 ± 0.57
3	Gentamicin ointment	20 mg/g	30 min	6	5.48 ± 2.21	6	1.55 ± 0.30
4	Gentamicin ointment	20 mg/g	Every 1 hour	6	4.09 ± 2.46	6	1.73 ± 0.29
5	Gentamicin ointment	20 mg/g	Every 2 hours	5	3.70 ± 1.88	6	2.10 ± 0.40
6	Gentamicin ointment	20 mg/g	Every 4 hours	—	—	5	2.12 ± 0.18
7	Gentamicin ointment	20 mg/g	Every 6 hours	6	6.07 ± 1.56	5	—

*1 vs 2, 4, or 5, $P \leq .01$; 1 vs 3 or 7, $P \geq .09$; 2 vs 3, 4, 5, or 7, $P \geq .06$; 3 vs 4, 5, or 7, $P \geq .19$; 4 vs 5 or 7, $P \geq .13$; 5 vs 7, $P = .05$.
†1 vs 2, 3, 4, 5, or 6, $P < .001$; 2 vs 3, 4, 5, or 6, $P \geq .11$; 3 vs 4, $P = .31$; 3 vs 5 or 6, $P \leq .03$; 4 vs 5, $P = .11$; 4 vs 6, $P = .03$; 5 vs 6, $P = .93$.

nism for its prolonged action is likely related to the repository effect of the ointment and the medication contained within.

Certain antibiotics in ointment vehicle have the potential for significant therapeutic effect. In short-term trials, commercial-strength gentamicin ointment was not as effective as commercial-strength gentamicin solution in reducing numbers of bacteria. This finding suggests that when compared to commercial-strength ointment, commercial-strength solution provides enhanced effect early in the course of treatment when the growth rate of the organism is maximal and penetration/bioavailability of the drug is critical. Fortified gentamicin ointment was as effective as fortified gentamicin solution when each was given every 30 minutes, and the fortified ointment continued to demonstrate a therapeutic effect at extended treatment intervals.

These findings may have significant clinical ramifications. The traditional treatment of bacterial keratitis includes the use of fortified topical antibiotic solutions given at frequent (30-minute) intervals. Frequency of administration is tapered with respect to clinical response, but it is unusual, at least in our experience, to lengthen the solution treatment interval for at least the first 48 hours in severe infectious bacterial keratitis. This frequency of administration is not without bothersome side effects, such as corneal and conjunctival toxicity. Effective extended treatment intervals would also provide for more efficient nursing care and enhance patient compliance.

The data suggest that fortified ointments in extended dose intervals may have significant clinical promise in the treatment of selected infections, but many questions, including information on corneal toxicity, measurable drug levels within the cornea and aqueous humor, commercial availability, and drug interactions, remain unanswered.

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Use of Split-Thickness Dermal Graft in the Surgical Treatment of Corneal and Scleral Defects

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We used split-thickness dermal grafts for the surgical treatment of corneal and scleral perforations in two patients and obtained excellent results. Patient 1 had severe lye burns and bilateral corneal perforations and Patient 2 had scleromalacia perforans. The dermal graft self-epithelializes and, thus, does not need to be covered by conjunctiva; is supple, without the bulkiness of other materials, particularly cartilage and periosteum; is hearty and flourishes on avascular surfaces such as cornea and sclera; has good tensile strength; and is autogenous.

A VARIETY OF TISSUES have been used in the surgical treatment of corneal and scleral perforations caused by necrotizing keratitis and scleritis.[1-9] Autogenous mucous membrane grafts were first recommended in the surgical treatment of scleromalacia perforans.[1] Later investigators[2,3] used autogenous auricular cartilage and homologous sclera, both of which are often covered by recipient conjunctiva to prevent necrosis of the grafted material.[4] These tissues are also bulky and often distort the underlying tissues when scarring occurs.

Several authors[5-8] have reported the successful use of fascia lata. However, when left exposed the fascia often breaks down and induces secondary scarring and distortion of host tissues. More recently, autogenous periosteum has been used.[9] This material, as with cartilage and homologous sclera, usually should be covered by conjunctiva. The periosteal graft has also been reported to undergo ossification.[10]

We report two cases (three eyes) in which we used autogenous split-thickness dermal grafts.

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One patient had bilateral severe lye burns of the corneas and the second patient had unilateral scleromalacia perforans.

Case Reports

Case 1

A 17-year-old boy suffered severe lye burns to both eyes, with sparing of the eyelids. Despite intensive medical therapy, including ocular lubricants, N-acetylcysteine, and oral vitamin C, he developed central corneal thinning, with almost total opacification of the cornea, dense cataracts, and iritis. Topical and periocular corticosteroids were judiciously administered. After four weeks of treatment, visual acuity was hand motions in both eyes. The conjunctivae were diffusely blanched. Intraocular pressure by pneumotonography was R.E.: 17 mm Hg and L.E.: 22 mm Hg. B-scan ultrasound showed no retinal detachment.

Because of an increasing fibrinous exudate in the anterior chamber, 60 mg of oral prednisone was instituted daily. Despite the frequent use of glass rods to break conjunctival adhesions, total bilateral symblepharon developed. The corneas continued to melt even with bilateral patching and the use of a bandage contact lens. It was believed that a corneal graft would not survive in the ischemic anterior segment. Medical treatment was continued under close observation in the hospital. It appeared that the eyes might eventually require evisceration.

Approximately seven weeks after the initial injury, a small perforation developed inferiorly in the right eye, with uveal prolapse. Because of the severe ischemia and corneal melting, we elected to use a split-thickness dermal graft to cover the perforation and protect the cornea from further melting.

The split-thickness dermal graft was harvested from the thigh using a power-driven Brown dermatome set at a depth of 12/1,000 to 15/1,000

inch. The graft was harvested by first removing the epidermal layer in a hinged fashion. The width of the dermatome was then reduced by approximately 8 mm on each side and the split-thickness dermal graft was harvested. Once the graft was obtained, the epidermal flap was repositioned and sutured in place. Fenestrations were cut in the flap to prevent the collection of fluid. This graft harvesting procedure has been previously described.[11]

A 360-degree peritomy was performed around the corneoscleral limbus. Corneal deepithelialization was not necessary because of the extensive necrosis. The graft was sized and then sutured to the conjunctival peritomy edges, and the eye was patched. The left eye was treated with a two-pillar permanent tarsorrhaphy.

Postoperatively, the graft was viable in the right eye and changed in color from white to a vascularized pink over several weeks. One week later, the tarsorrhaphy was opened on the left side; the cornea was still markedly thinned and opaque (Fig. 1, top left). The left eye showed inferior corneal stromal thinning with impending perforation despite the tarsorrhaphy. Therefore, a split-thickness dermal graft was used to cover the impending perforation (Fig. 1, top right). The graft took well and healed with a smooth mucosal surface within four weeks (Fig. 1, bottom left).

Eighteen months later, visual acuity was light perception in both eyes, with projection in the right eye (Fig. 1, bottom right). Symblepharon was present bilaterally. Mucous membrane reconstruction of the fornices was performed in the right eye, and a biopsy specimen of the split-thickness dermal graft was taken, which showed focal minimal keratinization in areas of exposure and lack of adenexal structures (Fig.

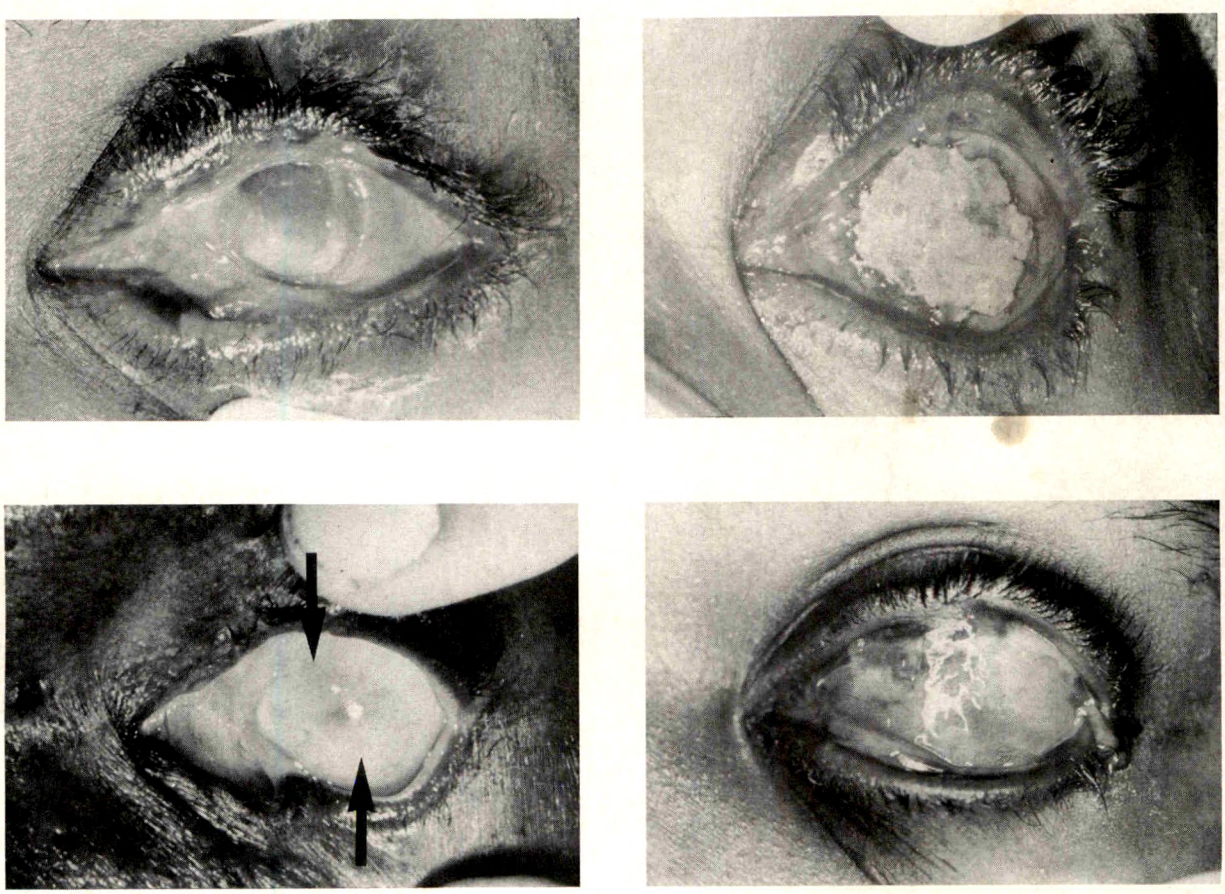


Fig. 1 (Mauriello and associates). Case 1, left eye. Top left, Impending corneal perforation inferiorly because of corneal lye burn. Top right, Split-thickness dermal graft sutured in place one week after surgery. Bottom left, One month after surgery. Note smooth mucosal surface. Arrows outline original graft site. Bottom right, Eighteen months after surgery.

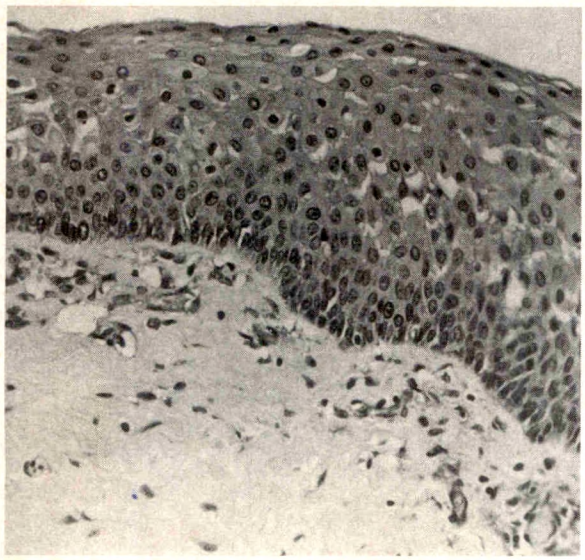


Fig. 2 (Mauriello and associates). Case 1. Biopsy specimen of split-thickness dermal graft taken 18 months after surgery shows no keratinization or keratohyaline granules and lack of adenexal structures (hematoxylin and eosin, ×160).

2). The patient will eventually undergo Cardonna implantation on the right side.

Case 2

A 70-year-old woman with a long history of disabling rheumatoid arthritis developed a sudden decrease in vision of the left eye after a coughing spasm. After the episode, she noted fluid leaking from the left eye. She had undergone extracapsular cataract extraction with posterior chamber implantation in the left eye four years previously. At that time visual acuity was L.E.: 20/30.

On our examination, visual acuity was R.E.: 20/200 because of cataract formation and L.E.: counting fingers at 5 feet. The right eye was unremarkable except for the cataract. The left eye showed significant eyelid edema and conjunctival injection. An area of scleromalacia perforans was present superotemporally from the 11 to the 3 o'clock meridians. A small scleral perforation, approximately 2 × 2 mm, was present (Fig. 3, left). The anterior chamber was shallow, with the posterior chamber intraocular lens in place. A dense membrane of lens remnants was present behind the posterior chamber intraocular lens. The pupil was middilated and sluggishly reactive to light. Visualization of the fundus was not possible.

Using a Brown dermatome set at 12/1,000 inch, a split-thickness dermal graft was taken from the right thigh. A 15 × 10-mm sized graft was used to cover the entire area of scleromalacia perforans after the necrotic and inflamed sclera and conjunctiva were excised. The dermal graft was laid onto the scleral bed and was sutured inferiorly to the cornea using 10-0 nylon sutures and superiorly to the conjunctival edges using 8-0 polyglactin.

Over the next several weeks, the ocular pain subsided and the anterior chamber reformed. Visual acuity was stable at counting fingers because of a dense membrane of lens capsular remnants. The split-thickness dermal graft was viable and showed no sign of infection (Fig. 3,



Fig. 3 (Mauriello and associates). Case 2. Left, Superior scleral perforations in patient with scleromalacia perforans (arrows). Right, Split-thickness dermal graft four weeks after surgery.

right). The findings were unchanged six months after surgery.

Discussion

We advocate the use of dermal grafts, which we believe may be superior to similarly used tissues (autogenous fascia lata, periosteum, cartilage, and homologous sclera), in the repair of perforations caused by necrotizing scleritis and keratitis. The split-thickness dermal graft has characteristics that make it suitable for use as a scleral or corneal patch graft. First, the dermal graft is of sufficient thickness to form a good seal when covering perforations. Second, the dermal tissue undergoes self-epithelialization and does not necrose when left exposed. Substitute materials, such as autogenous fascia lata, periosteum, or cartilage, when not covered by conjunctiva may necrose. Self-epithelialization is a distinct advantage of dermal grafts since, in some patients, conjunctiva is not always available and cannot be mobilized (as in Patient 1). Epithelialization of the graft occurs not only from the host tissues but also from the epithelium of the skin appendages of the dermal graft and, importantly, a nonkeratinizing epithelium is produced.[11]

Third, the dermal graft is supple and does not form a bulky irregular surface as does buried cartilage or periosteum. Fourth, the graft is hearty and survives on avascular surfaces such as bone after exenteration.[11] Fifth, the graft has excellent tensile strength. Finally, dermal grafts are autogenous, and thus are not antigenic.

In our Patient 1, who had severe corneal lye burns, the dermal graft was also used as a substitute for mucous membrane. In this case, symblepharon formed after surgery. However, a recent case report demonstrated the successful use of the dermal graft in reconstructing the socket.[12]

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Long-Term Corneal Endothelial Changes After Intraocular Lens Implantation

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We studied the morphologic characteristics of the corneal endothelium in a series of patients who had undergone phacoemulsification with intraocular lens implantation performed by one surgeon. Specular microscopy and computer-assisted morphometry were performed preoperatively and three years after surgery. Nineteen eyes that received posterior chamber lenses with intracapsular fixation had a mean endothelial cell loss of 18.1%, without any significant change in cell size (polymegethism) or shape variability (pleomorphism). Implantation of anterior chamber lenses with the posterior capsule left intact (18 eyes) caused a similar degree of cell loss (23.5%) but caused marked polymegethism and pleomorphism of the cells. Endothelial cell loss (28.5%) and morphologic changes were greatest in five eyes that received anterior chamber lenses because of a rupture of the posterior capsule.

ALTHOUGH POSTERIOR CHAMBER lens implantation has become the most common method for correction of aphakia, a number of surgeons continue to use anterior chamber lenses.[1] The long-term effects of these intraocular lenses on the corneal endothelium are of great concern because of the corneal edema caused by continuing endothelial cell loss after the insertion of some of the early models of intraocular lenses.[2,3]

Several authors have reported that endothelial cell density in the central cornea stabilizes within three months after intracapsular or extracapsular lens extraction alone.[4-9] Conversely, there are conflicting reports of stabilization of endothelial cell density, or of continuing cell loss after anterior or posterior chamber lens implantation even if the postoperative course is uncomplicated.[6-8,10] The discrepancies in these reports may be the result of differences in the age of patients, method of cataract removal, type of lens implants used, and location of intraocular implant.

Recent studies have demonstrated that quantitative measurements of cellular structure (polymegethism and pleomorphism) are more sensitive indications of endothelial damage and function than changes in cell density.[11-16] Matsuda, Suda, and Manabe[17] and Schultz and associates[18] found that while endothelial cell density decreased rapidly and cellular structure was altered in the first month after a simple cataract extraction, the rate of cell loss decreased between three and six months postoperatively as the cellular pattern returned to normal. Similar endothelial changes have been noted in patients undergoing posterior chamber lens implantation.[18] Glasser and associates,[19] however, reported the persistence of endothelial morphologic abnormalities more than one year after anterior chamber lens implantation.

In the preceding studies, anterior chamber lenses were often implanted after intracapsular lens extraction, while posterior chamber lenses were inserted after extracapsular cataract extraction or phacoemulsification. Therefore, two major variables exist for the eyes with these intraocular lenses: the location of the lens loops and the postoperative condition of the posterior capsule. These variables make comparison of the published data difficult. Consequently, this randomized controlled study was undertaken to evaluate the morphologic characteristics of the corneal endothelium in two different groups of patients who underwent phacoemulsification with insertion of either posterior or anterior chamber lenses, with the posterior

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capsule left intact. An additional group who received anterior chamber lenses because of an intraoperative break in the posterior capsule was also studied in a nonrandomized fashion.

Material and Methods

We assigned candidates for cataract surgery by random number selection to undergo either posterior (Group 1) or anterior (Group 2) chamber lens implantation after pupillary plane phacoemulsification,[20] with the posterior capsule left intact. The phacoemulsification was chosen because the degree of surgical trauma can be controlled and has yielded good results. Group 1 consisted of 19 eyes from 18 patients, all of whom received original (Iolab style 105 B) or modified J-loop lenses (Iolab style 103 N), with the lens loop placed in the capsular bag. Group 2 comprised 18 eyes from 18 patients. Seventeen eyes received semiflexible closed-loop anterior chamber lenses with four-point fixation (Intermedics model 24) and one received a flexible open-loop lens (American Medical Optics model AC-41). We also studied five eyes from five patients who underwent anterior chamber lens implantation because inadvertent rupture of the posterior capsule prevented the insertion of posterior chamber lenses (Group 3). In this group, four semiflexible closed-loop (Intermedics model 24) and one flexible open-loop (American Medical Optics model AC-41) lenses were implanted after anterior vitrectomy was performed with a vitreous cutter.

We excluded patients who were diabetic or who had a history or current signs of ocular diseases other than cataract. Only patients with no surgical or postoperative complications, except for the rupture of the posterior capsule in Group 3, were included in the study. The same inclusion and exclusion criteria were used for each group.

All surgeries were performed by one of us (K.M.), with the same medications. The surgical procedures used have been previously described.[21] Balanced Salt Solution (BSS) was used to irrigate the eye during surgery. To maintain mydriasis during surgery, 0.1 ml of 1:1,000 epinephrine was added to a 500-ml bottle of BSS. In all cases, 1% sodium hyaluronate (Healon) was injected before lens implantation and was later aspirated from the anterior chamber. Postoperative medications, including oral and topical antibiotics and topical corticosteroids, were given in the same fashion to all patients as previously described.[21]

The endothelium of the central cornea was examined and photographed with a specular microscope a few days before and three years after surgery. Approximately five to ten photographs were taken of each cornea. The photographs with good cell boundaries were used for analysis. An independent examiner performed all tracing and digitization. A total of 100 cells were traced and analyzed with a computerized digitizer, as previously described.[11,12] Endothelial structure was evaluated by measuring a variety of factors, including cell density (cells/mm^2), coefficient of variation in cell size (an objective measure of polymegethism), and percentage of hexagonal cells (an index of pleomorphism). Cell loss was expressed as a percentage of the preoperative cell density.

Differences were considered statistically significant if parametric (two-sided Student *t*-test) and nonparametric (two-sided Wilcoxon two-sample test) tests yielded a P value of less than .05.

Results

There were no significant differences in age, sex, length of postoperative period, ultrasound time during phacoemulsification, or amount of intraocular irrigating solution used among the three groups of patients studied (Table 1).

TABLE 1
CLINICAL DATA OF PATIENTS (MEAN ± S.D.)

CLINICAL DATA	GROUP 1*	GROUP 2†	GROUP 3‡
No. of eyes	19	18	5
Sex			
Male	6	6	0
Female	12	12	5
Age (yrs)	72.4 ± 5.3	73.1 ± 8.4	73.0 ± 5.6
Postoperative period (mos)	41 ± 3	41 ± 2	39 ± 2
Ultrasound time (min)	1.6 ± 0.5	1.6 ± 0.4	1.8 ± 0.3
Infusion volume (ml)	131 ± 26	135 ± 29	143 ± 24

*Group 1: implantation of posterior chamber lenses with intracapsular fixation.

†Group 2: implantation of anterior chamber lenses with intact posterior capsule.

‡Group 3: implantation of anterior chamber lenses with ruptured posterior capsule.

TABLE 2
ENDOTHELIAL MORPHOLOGIC DATA (MEAN ± S.D.)

GROUP	CELL DENSITY (CELLS/MM^2)	CELL LOSS (%)	COEFFICIENT OF VARIATION	HEXAGONAL CELLS (%)
Group 1				
Preoperative	3,098 ± 300	—	0.300 ± 0.051	61.2 ± 9.4
Postoperative	2,531 ± 316*	18.1 ± 8.9	0.304 ± 0.056	61.9 ± 6.6
Group 2				
Preoperative	3,141 ± 263	—	0.313 ± 0.055	62.3 ± 6.1
Postoperative	2,438 ± 479*	23.5 ± 12.8	0.362 ± 0.085*†	57.4 ± 4.8*†
Group 3				
Preoperative	3,086 ± 225	—	0.296 ± 0.033	62.3 ± 6.1
Postoperative	2,211 ± 434*†	28.5 ± 12.8†	0.365 ± 0.044*†	51.6 ± 6.7*†‡

*$P < .05$ compared with preoperative value.

†$P < .05$ compared with Group 1.

‡$P < .05$ compared with Group 2.

These groups were also comparable in terms of preoperative endothelial status, including cell density, coefficient of variation in cell size, and percentage of hexagonal cells (Table 2).

As shown in Table 2, the eyes in Group 1 lost significantly fewer endothelial cells (mean ± S.D., 18.1% ± 8.9%) than those in Group 3 (28.5% ± 12.8%). Group 2 had a mean cell loss of 23.5% ± 12.8%, which was not significantly different from the cell loss seen in Groups 1 or 3.

At the three-year follow-up visit, the endothelium of Group 1 showed no significant change in the coefficient of variation in cell size and percentage of hexagonal cells. Eyes in both Groups 2 and 3, however, had a significantly higher coefficient of variation and a marked reduction in the percentage of hexagonal cells when compared to their respective preoperative values. These morphologic changes were also significantly greater than those seen in Group 1. Moreover, the percentage of hexagonal cells was markedly lower in Group 3 compared to Group 2, although no statistical difference in the coefficient of variation was found between the two groups.

Discussion

During a mean follow-up period of over three years, we found that the eyes with posterior chamber lenses with intracapsular fixation (Group 1) had fewer changes in the corneal endothelium than those that received anterior chamber lenses with (Group 2) or without (Group 3) an intact posterior capsule. The endothelial changes in Group 3 were also significantly greater than those seen in Group 2.

The endothelial cell loss for Group 1 compared favorably with the results of other studies.[8,10] Despite this reduction in cell count, no significant changes in polymegethism or pleomorphism were noted three years after surgery. Matsuda, Suda, and Manabe[17] and Schultz amd associates[18] reported that endothelial cell loss stabilizes and the cells return to a normal morphologic configuration within three months after intracapsular or extracapsular cataract extraction, with or without posterior chamber lens implantation. Recent reports have also shown that morphologic changes are more sensitive indicators of endothelial damage and function than changes in cell density.[11-16] These findings suggest that endothelial remodeling had already taken place in Group 1 and there may be no long-term or continuing damage to the corneal endothelium in this group.

The major difference between Groups 1 and 2 was the location of the lens implant used. There was no statistical difference in cell loss between the two groups. The endothelium of Group 2, however, was found to have marked polymegethism and pleomorphism postoperatively as compared to that of Group 1. These differences suggest that the location of lens

loops may affect the long-term morphologic stability of the corneal endothelium after surgery, and that anterior chamber lenses may retard the endothelial remodeling that normally occurs in eyes that received posterior chamber lenses with intracapsular fixation. The reasons for this are not clear but may be related to chronic irritation of the angle causing a low-grade or subclinical inflammation,[2,6,22,23] which may be associated with the disruption of the blood-aqueous barrier after surgery. Miyake and associates[24,25] reported that a significant breakdown of the blood-aqueous barrier persists more than three years after anterior chamber lens implantation, while the barrier function is reestablished within one year after surgery in eyes with posterior chamber lenses with intracapsular fixation.

A recent report has demonstrated that endothelial cell loss and morphologic changes were no different after intracapsular than after extracapsular cataract extraction,[18] suggesting that the retention of the posterior capsule does not affect the endothelium in aphakic eyes without lens implants. In this study, however, we found that the endothelium of Group 3 had greater pleomorphism than that of Group 2 after surgery, despite no statistically significant differences in cell loss or polymegethism between the two groups. It appears, therefore, that the absence of the posterior capsule, which presumably acts as a physiologic barrier between the anterior and posterior segments, may have an adverse effect on the corneal endothelium in eyes with anterior chamber lenses. A similar finding has been reported by Binkhorst, Loones, and Nygaard.[26]

The persistent morphologic changes noted in Groups 2 and 3 were comparable to those reported by Glasser and associates[19] more than one year after intracapsular lens extraction with anterior chamber lens implantation. Because most lens implants used in both studies were of the semiflexible closed-loop style, it remains unknown whether such endothelial changes are specific for these lenses or can be seen in other anterior chamber lenses with different designs. Moreover, the clinical significance of the observed endothelial abnormalities remains unclear. However, it has been suggested that polymegethism and pleomorphism are indicative of low functional reserve of the monolayer[12-15] and may be an early sign of continuing cell loss.[12,27,28] Therefore, the persistent endothelial morphologic changes noted in our study may at least partly explain the findings of recent studies that the number of eyes with semiflexible closed-loop anterior chamber lenses suffering from decreased vision caused by corneal edema is now increasing.[29-31] Further morphometric studies are needed to evaluate the effects that various intraocular lenses of different designs, materials, and fixation sites have on the long-term corneal endothelial viability. The results can be used to predict early endothelial instability, which may be associated with subsequent irreversible corneal edema.

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OPHTHALMIC MINIATURE

The cornea of her left eye was scarred by measles, but no one knows that yet. She sees well enough to be aware of the street, and to know she hates and fears it. Sometimes, when the sunlight makes everything shimmer in front of her, she pretends she is on a different street, one she saw long ago.

Marilyn French, *Her Mother's Daughter*
New York, Summit Books, 1987, p. 31

Predictors of Scleral Rupture and the Role of Vitrectomy in Severe Blunt Ocular Trauma

Stephen R. Russell, M.D., Karl R. Olsen, M.D., and James C. Folk, M.D.

We reviewed retrospectively 40 eyes that had received blunt trauma and had been explored for scleral rupture. Twenty-nine eyes had scleral rupture. Of these 29, ten had ruptures seen preoperatively. Nineteen had occult ruptures. The preoperative findings predictive of scleral rupture were a visual acuity of light perception or no light perception, an intraocular pressure of less than 10 mm Hg, hyphema, and chemosis. Of the 29 ruptures, 27 involved the superior hemisphere and 25 involved the anterior hemisphere of the globe. Ten of 29 eyes (34%) with scleral rupture and eight of 11 eyes (73%) without rupture achieved a final visual acuity of 5/200 or better over an average follow-up period of 6.7 months. Factors prognostic of ambulatory vision for eyes with ruptured and intact globes included an initial visual acuity of 5/200 or better, absence of scleral rupture, and a rupture length of less than 11 mm in eyes with ruptures. The vitrectomized eyes also had a better result, suggesting that early pars plana vitrectomy is of benefit in selected rupture cases.

SEVERE BLUNT TRAUMA to the eye can be difficult to manage. Occult ruptures are of greatest concern, since the failure to diagnose and repair them promptly may worsen an already guarded prognosis. We performed a retrospective study on 40 eyes that had received severe blunt trauma and were then explored for a possible scleral rupture. We hoped to clarify which initial ocular signs were important in predicting the presence of a rupture. Previous work by Cheery[1-3] and Riffenburgh[4] evaluated only those traumatized patients with globe rupture and did not include any eyes without ruptures that had been explored. We believed analysis of all explored eyes was important because it would alert the physician to those high-risk features[1,2] warranting surgical investigation. It would also clarify which eyes have a low risk of harboring a scleral rupture and, therefore, do not require immediate surgical intervention.

Our study was also performed to confirm or refute previous work detailing the usual location of scleral rupture.[1,2] Such information allows the clinician to direct the initial exploration to areas where an occult scleral rupture is most likely. The rupture could then be identified and sutured promptly, minimizing extraneous manipulations of the eye, which may increase the risk of additional prolapse of intraocular contents. Finally, we studied which ocular factors[3] were predictive of the ultimate visual outcome and whether a pars plana vitrectomy could improve this result.

Material and Methods

The operative records of Bascom Palmer Eye Institute from Jan. 1, 1982 to Dec. 31, 1985 were reviewed retrospectively by one of us (S.R.R.) to select eyes that had received severe blunt trauma and were explored for a scleral rupture. Eyes were only included if the initial exploratory operation was performed at the Bascom Palmer Eye Institute. Eyes that did not undergo operative procedures would thus be excluded. All eyes had acute ruptures occurring within 24 hours of examination at Bascom Palmer. Echography, when performed, was under the supervision of a full-time echographer. Adequate standarized A-scan and contact B-scan ultrasonography was not available before 1982,

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From the Bascom Palmer Eye Institute, Department of Ophthalmology, University of Miami, Miami, Florida (Drs. Russell and Olsen) and the Department of Ophthalmology, University of Iowa, Iowa City, Iowa (Dr. Folk). This study was read in part before the 22nd Annual Resident's Days, June 21, 1986, Key Biscayne, Florida.

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thereby limiting expanded retrospective review. Eyes were excluded if they had a corneal rupture or any condition associated with weakened sclera such as severe myopia, congenital glaucoma, scleritis, or prior ocular surgery. Eyes were also excluded if they were explored for presumed penetrating trauma or if the patient had been injured during a motor vehicle accident and was known to have glass on his face or in the conjunctival fornices. All 40 eyes that met these criteria were included in the study.

Two 3-year-old patients were too young to read the Snellen chart. Both had central, steady, and maintained fixation and were included in the study. Statistical analysis was performed using the chi-square test or Fisher's exact test, as appropriate. Prior approval for this study was obtained from the University of Miami Medical Sciences subcommittee for the protection of human subjects.

Results

In ten of the 40 eyes, the scleral rupture could be seen on initial examination. Although a rupture was suspected in the remaining 30 eyes, no rupture was seen on the preoperative examination. Surgical exploration disclosed ruptures in 19 of these eyes. These three groups of eyes, those with visible evidence of rupture, occult rupture, and no rupture, were analyzed separately unless otherwise noted.

Factors predictive of a scleral rupture—Eyes with scleral ruptures had a worse visual acuity on initial examination than eyes without ruptures (Tables 1, 2, and 3; $P < .003$). Sixteen of 19 eyes that had an occult rupture (Table 1) and eight of ten eyes that had a rupture seen on the initial examination (Table 2) had an initial visual acuity of only light perception or no light perception. Conversely, seven of the 11 eyes without ruptures (Table 3) had ambulatory (5/200 or better) initial visual acuity. Only three of 11 nonruptured eyes had an initial visual acuity of light perception or no light perception.

Eyes with ruptures also had a lower intraocular pressure on the initial examination ($P < .02$). In eyes with an occult scleral rupture found on exploration, ten of 17 eyes in which the pressure was measured had an intraocular pressure of 0 mm Hg and only five of 17 had an intraocular pressure of 10 mm Hg or more. The intraocular pressure was measured in six of ten eyes in which a rupture could be seen on the initial examination and five of six had a pressure of 0 mm Hg. In eyes without scleral ruptures, however, eight of nine in which the pressure was measured had values of 10 mm Hg or more, with the remaining eye having an intraocular pressure of 2 mm Hg.

Eyes with ruptures also more often had hyphemas ($P < .02$). The presence or absence of hyphema was noted in 18 of 19 eyes with an occult scleral rupture and nine of ten eyes with a rupture seen on the initial examination. Fifteen of 18 and eight of nine of these ruptured

TABLE 1
EYES WITH RUPTURE NOTED PREOPERATIVELY*
(N = 10)

PATIENT NO.	INITIAL VISUAL ACUITY†	CHEMOSIS	INTRAOCULAR PRESSURE (MM HG)	HYPHEMA	RUPTURE SIZE (MM)	VITRECTOMY	FINAL VISUAL ACUITY†	FOLLOW-UP (MOS)	ENUCLEATION
1	20/100	Yes	10	Yes	4	No	20/20	9	No
2	5/200	No	NR	No	10	No	20/30	3	No
3	LP	Yes	0	Yes	15	No	CF	1	No
4	LP	Yes	0	Yes	15	No	CF	3	No
5	LP	Yes	0	Yes	20	No	LP	9	No
6	LP	Yes	0	Yes	25	No	LP	10	No
7	NLP	Yes	NR	Yes	12	No	LP	2	No
8	LP	Yes	NR	NR	18	No	NLP	3	Yes
9	NLP	Yes	0	Yes	NR	No	NLP	1	Yes
10	NLP	Yes	NR	Yes	29	No	NLP	3	Yes

*NR, not recorded.
†CF, counting fingers at less than 5 feet; LP, light perception; NLP, no light perception.

TABLE 2
EYES WITH OCCULT RUPTURES*
(N = 19)

PATIENT NO.	INITIAL VISUAL ACUITY†	CHEMOSIS	INTRAOCULAR PRESSURE (MM HG)	HYPHEMA	RUPTURE SIZE (MM)	VITRECTOMY	FINAL VISUAL ACUITY†	FOLLOW-UP	ENUCLEATION
1	LP	No	28	Yes	7	Yes	20/30	3 yrs	No
2	LP	Yes	9	Yes	30	Yes	20/50	10 mos	No
3	LP	Yes	0	Yes	18	Yes	20/50	20 mos	No
4	LP	Yes	0	Yes	35	Yes	20/80	10 mos	No
5	LP	Yes	0	Yes	18	Yes	20/200	8 mos	No
6	LP	Yes	14	Yes	5	Yes	5/200	2 yrs	No
7	LP	Yes	0	Yes	17	Yes	HM	7 mos	No
8	LP	Yes	0	Yes	17	Yes	HM	1 mo	No
9	NLP	Yes	NR	Yes	20	Yes	NLP	1 mo	Yes
10	CSM	No	16	Yes	4	No	20/20	7 mos	No
11	CF	No	0	No	3	No	20/200	4 mos	No
12	HM	Yes	9	No	16	No	CF	2 mos	No
13	LP	Yes	21	Yes	4	No	CF	2 yrs	No
14	LP	No	17	Yes	15	No	LP	1 mo	No
15	LP	Yes	0	No	29	No	LP	8 mos	No
16	LP	Yes	NR	Yes	20	No	NLP	2 mos	Yes
17	LP	Yes	0	Yes	12	No	NLP	6 mos	Yes
18	NLP	Yes	0	NR	35	No	NLP	8 mos	Yes
19	NLP	No	0	Yes	16	No	NLP	1 mo	No

*NR, not recorded.
†CF, counting fingers at less than 5 feet; HM, hand motions; LP, light perception; NLP, no light perception; CSM, central, steady, maintained.

eyes had hyphemas. Only four of 11 nonruptured eyes had hyphemas. The presence of a hemorrhagic chemosis was also slightly increased in eyes with scleral ruptures ($P < .03$). Fourteen of 19 eyes with occult ruptures had chemosis. Nine of ten eyes that had visible ruptures initially also had chemosis. Only five of 11 eyes without ruptures had chemosis.

TABLE 3
EYES WITH NO RUPTURE FOUND*
(N = 11)

PATIENT NO.	INITIAL VISUAL ACUITY†	CHEMOSIS	INTRAOCULAR PRESSURE (MM HG)	HYPHEMA	RUPTURE SIZE (MM)	VITRECTOMY	FINAL VISUAL ACUITY†	FOLLOW-UP (MOS)
1	20/30	No	12	No	No	No	20/20	2
2	20/30	No	26	No	No	No	20/20	2
3	20/50	No	14	No	No	No	20/20	5
4	20/80	No	16	No	No	No	20/20	7
5	LP	No	NR	No	No	No	20/20	3
6	CSM	Yes	NR	No	No	No	20/50	1
7	LP	Yes	47	Yes	No	Yes	20/50	3
8	20/200	Yes	12	Yes	No	No	20/200	8
9	HM	Yes	12	Yes	No	No	HM	2
10	LP	No	2	Yes	No	Yes	HM	7
11	5/200	Yes	15	No	No	No	LP	9

*NR, not recorded.
†CSM, central, steady, maintained; HM, hand motions; LP, light perception.

Other factors that did not appear to be predictive of the presence of a scleral rupture included anterior chamber depth, eyelid edema or ecchymosis, eyelid laceration, abnormal ductions, corneal folds, retinal detachments, or vitreous hemorrhage.

Seventeen patients underwent preexploration ultrasound. A rupture was diagnosed by ultrasound in three of 13 patients who did indeed have ruptures and in one of four patients who did not have a rupture.

Location and size of ruptures—In the 29 patients who had a scleral rupture, the defect was anterior to the equator in 12 eyes (41%), spanning the equator in 13 eyes (45%), and posterior in four eyes (14%). The direction of the rupture was noted in 25 eyes. Seven of these 25 had a radially oriented rupture (perpendicular to the corneoscleral limbus). Nine eyes had a circumferentially oriented rupture (parallel to the corneoscleral limbus). The nine other ruptures were oriented both radially and circumferentially. The location of the rupture was noted in 22 eyes. The rupture occurred superiorly in 18 of these 22 eyes (Figure). All eyes had only one rupture.

Outcome—Eyes without scleral ruptures had a significantly better final visual acuity than eyes with ruptures ($P < .01$, Mann Whitney rank test). Eight of 11 eyes without ruptures had a final visual acuity of ambulatory vision (5/200 or better). Only eight of 19 eyes with occult scleral ruptures and two of ten eyes with ruptures seen initially had a final visual acuity of 5/200 or better. In the eyes with ruptures, the final visual acuity correlated inversely to the length of the rupture. Six of seven eyes with ruptures less than 11 mm achieved a visual acuity of 5/200 or better, whereas only five of 22 eyes with ruptures larger than 12 mm achieved this same visual acuity ($P < .012$).

None of the eyes that had a scleral rupture seen initially underwent pars plana vitrectomy. Two of the 11 unruptured eyes did have a vitrectomy and one of these did well, with a final visual acuity of 20/50. The most useful comparison, however, involves the 19 eyes that had an occult scleral rupture. Three of these 19 eyes had an initial visual acuity of no light perception. Of the remaining 16 eyes, eight underwent pars plana vitrectomy. Final visual acuity in the vitrectomized group (Patients 1 through 8) compared favorably to that in the group that did not undergo vitrectomy (Patients 10 through 17) (Table 2). On balance, the vitrectomized eyes had a slightly worse initial visual acuity, more often had hyphema, and tended to have a slightly larger rupture size. Only two of eight eyes that did not undergo vitrectomy had a final ambulatory visual acuity, whereas six of eight eyes that did undergo vitrectomy achieved ambulatory or better vision.

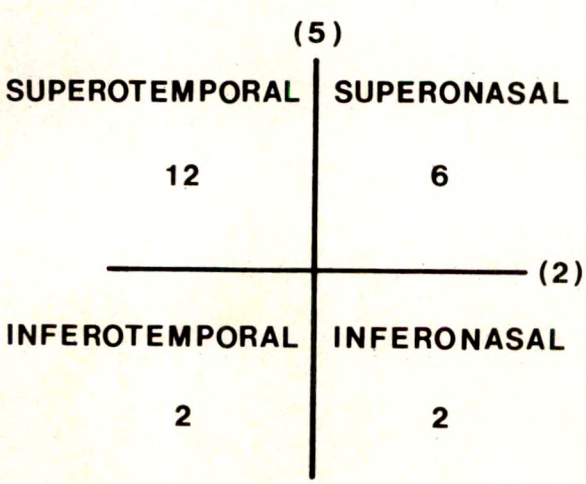


Figure (Russell, Olsen, and Folk). Location of scleral ruptures. The number in each quadrant indicates the frequency of respective single quadrant ruptures. Numbers between quadrants (in parentheses) represent rupture involvement of both adjacent quadrants. No rupture involved more than two quadrants. The optic nerve was the posterior landmark used in dividing the quadrants.

Discussion

Important predictors for the presence of a scleral rupture on the initial examination included initial visual acuity and intraocular pressure. All but four of 30 eyes with ruptures had a visual acuity of light perception or no light perception. Conversely, only three of 11 eyes without ruptures had a visual acuity that was this poor, and seven of 11 had ambulatory or better vision. All but one eye without rupture had an initial intraocular pressure of 10 mm Hg or above, whereas only five of 17 eyes with occult ruptures and one of six with visible ruptures had pressures this high. Additionally, an intraocular pressure of 0 mm Hg was recorded in ten of 17 eyes with occult ruptures and five of six eyes with visible ruptures. Eyes with ruptures more often showed hemorrhagic chemosis and hyphemas.

Although there was no single factor from this study that was absolutely predictive of scleral rupture, our information is useful in guiding a clinician to explore or observe a traumatized eye. All eyes with intraocular pressures of less

than 10 mm Hg should be explored because nearly all of them will have a scleral rupture. However, about one quarter of eyes with ruptures will have an intraocular pressure of 10 mm Hg or more. The initial visual acuity is also a helpful indicator because only two of 29 ruptured eyes had an initial visual acuity of 5/200 or better. In both of these eyes, the rupture could be seen clinically. Therefore, if an eye has a visual acuity that can be measured on the Snellen chart and an intraocular pressure of 10 mm Hg or greater, the risk of surgical exploration may outweigh the benefits and the eye can be observed clinically. In these eyes the chance of a scleral rupture is minimal.

Scleral ruptures were diagnosed by preoperative ultrasound in three of 13 patients (23%) who had ruptures. These disappointing results are probably a result of the difficult examination when performed through markedly swollen eyelids and the anterior location of many ruptures. Recently, an echographic sign has been described[5] as diagnostic for scleral rupture that may improve examination sensitivity and specificity.

If no rupture is seen on the preoperative examination, the surgeon should first explore the superotemporal quadrant followed by the superonasal quadrant and then either of the inferior quadrants. None of the eyes that received blunt trauma had more than one scleral rupture. Therefore, once a rupture is repaired, no further exploration of the sclera is necessary.

As expected, eyes with ruptures had a poorer outcome than eyes without ruptures. Eyes with larger ruptures also did more poorly than eyes with smaller ruptures. Eyes that underwent pars plana vitrectomy did much better than eyes that did not undergo vitrectomy, suggesting that vitrectomy improves outcome. Criticisms of the apparent advantages of pars plana vitrectomy could include biases of retrospective data collection such as failure to detect hemorrhagic retinal or choroidal detachment or concomitant macular or optic nerve damage. Certainly these other factors would worsen the visual prognosis and may have influenced the treating ophthalmologist not to perform a vitrectomy. A careful review of the records, however, did not show any such bias. As mentioned previously, the vitrectomized eyes appeared to have had worse preoperative visual acuities and larger ruptures. A second criticism is the limited follow-up time. Follow-up was particularly short for those eyes that did not receive vitrectomy. However, two of four eyes with less than six months of follow-up already had a visual acuity of no light perception and would not be expected to improve. Because of the limitations of a retrospective study on a moderate number of patients, the apparent beneficial effect of pars plana vitrectomy can only be considered suggestive.

It is certainly plausible that pars plana vitrectomy should improve the visual prognosis in some eyes with scleral ruptures. Eyes with scleral penetration and intraocular blood are predisposed to proliferative vitreoretinopathy and scar proliferation and contraction, as documented in experimental models of penetrating trauma.[6] Vitrectomy can remove the blood along with the proliferating elements and increase the likelihood of an improved anatomic and visual result.[7] This conclusion is supported by the observation that none of the nonvitrectomized eyes with ruptures larger than 12 mm did well, whereas four of six vitrectomized eyes with large ruptures achieved ambulatory or better visual acuity. With improved instrumentation and greater surgical experience, more extensive pars plana vitrectomies can now be performed with fewer complications. Therefore, we believe that vitrectomy should be performed in these eyes in the early posttraumatic period (five to 14 days) unless strong contraindications exist.

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Maternal Corneal Thickness During Pregnancy

Robert N. Weinreb, M.D., Arthur Lu, M.D., and Charles Beeson, M.D.

We measured central corneal thickness in 89 pregnant women. It was increased 16 μm (P = .01) compared to the control eyes of 18 nongravid and 17 postpartum women. There was no significant difference (P = .79) in corneal thickness between the nongravid and postpartum groups. When comparing subjects by week of gestation, there was no trend over time in corneal thickness (analysis by linear regression). Intraocular pressure was lowered during pregnancy, but it did not correlate with corneal thickness for either the pregnant or nonpregnant group.

PREGNANT WOMEN often cannot tolerate contact lens wear.[1,2] It has been hypothesized that this may be related to changes in corneal sensitivity resulting from increased corneal thickness or altered tear composition.[3-5] Millidot[3] described five pregnant women with increased corneal thickness who also had decreased corneal sensation. Manchester[6] examined 27 women in the third trimester of pregnancy and again six weeks postpartum. Using an optical pachymeter, he demonstrated that corneal thickness decreased 0.2% after delivery. In this study, we compared the central corneal thickness throughout each trimester of pregnancy with corneal thickness in nonpregnant control subjects.

Subjects and Methods

Pregnant women and nonpregnant female control subjects seen in the Obstetrics and Gynecology Clinic at our institution for routine examinations were enrolled in this study. The study was approved by the Human Subjects Committee and informed consent was obtained. Eighty-nine consecutive pregnant women and 35 nonpregnant control subjects were examined. The control group consisted of 18 nongravid and 17 postpartum subjects. Postpartum subjects were evaluated within six weeks after delivery. The average age was 23 years for the pregnant group and 27 years for the nonpregnant group.

One drop of 0.5% proparacaine hydrochloride was administered to each eye for topical anesthesia. While the patient was seated, three separate readings of central corneal thickness were obtained with an ultrasound pachymeter. The mean of the three readings was calculated for each eye. To avoid possible diurnal variations of corneal thickness, readings were taken between 11:00 A.M. and 3:00 P.M. Intraocular pressure was then measured with a pneumatonometer.

Corneal thickness of pregnant and nonpregnant subjects was compared by unpaired *t*-tests. Corneal thickness of nongravid and postpartum subjects also was compared by unpaired *t*-tests. Linear regression was used to analyze corneal thickness of pregnant subjects according to weeks of gestation. The relationship between corneal thickness and intraocular pressure was examined with Pearson correlations. $P < .05$ was considered significant.

Results

In nongravid control eyes, corneal thickness was R.E.: 535.5 ± 34.8 μm (mean ± S.D.) and L.E.: 533.4 ± 36.5 μm. In the postpartum group, corneal thickness was R.E.: 532.5 ± 27.0 μm and L.E.: 532.7 ± 26.8 μm. The difference between these two groups for either the right or left eye was not statistically significant.

In the pregnant subjects, mean corneal thickness was R.E.: 550.7 ± 34.1 μm and L.E.: 550.8 ± 34.1 μm (Table 1). Differences between preg-

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TABLE 1
CENTRAL CORNEAL THICKNESS (MEAN ± S.D.) WITH PREGNANCY

	PREGNANT SUBJECTS (N = 89)		CONTROL SUBJECTS (N = 35)	
	R.E.	L.E.	R.E.	L.E.
Corneal thickness (μm)	550.7 ± 34.1	550.8 ± 34.1	534.0 ± 30.9	533.0 ± 31.7
Intraocular pressure (mm Hg)	14.8 ± 2.3	14.6 ± 2.4	16.1 ± 2.4	16.2 ± 2.5

nant and control subjects were statistically significant for both right and left eyes ($P < .02$). The mean corneal thickness in the right eye was highly correlated with corneal thickness in the left eye ($P < .01$). Corneal thickness did not correlate with age.

We then divided the pregnant subjects into three groups based on weeks of gestation. Subjects examined during the first 13 weeks of gestation were included in the first trimester group, those between 13 and 27 weeks were in the second trimester group, and those after 27 weeks were in the third trimester group. By linear regression, there was no trend over time in corneal thickness in either eye (Table 2). From these data, we found that corneal thickness increases by 3% (16 μm) during pregnancy, independent of the stage of gestation, and returns to baseline levels within a few weeks after delivery.

Intraocular pressure in pregnant subjects was lower than in control eyes (Table 1). There was no correlation between corneal thickness and intraocular pressure.

Discussion

Our data indicate that central corneal thickness is 3% higher in the eyes of pregnant women compared with the control eyes. This difference is statistically significant. The increase in corneal thickness did not change during the gestation period and it returned to baseline level within a few weeks after delivery.

TABLE 2
CENTRAL CORNEAL THICKNESS (MEAN ± S.D.) OF PREGNANT SUBJECTS

	CORNEAL THICKNESS (μM)	
TRIMESTER	R.E.	L.E.
First (n = 19)	549.3 ± 35.9	551.5 ± 34.9
Second (n = 26)	546.7 ± 29.5	545.3 ± 28.4
Third (n = 44)	554.0 ± 36.5	554.1 ± 37.4

These observations support the hypothesis that hormonal changes during pregnancy lead to retention of water in the cornea, with a concomitant increase in corneal thickness as well as alteration in corneal topography. In response to the rapidly growing fetus and placenta and their increasing demands, the pregnant woman undergoes numerous, intense metabolic changes.[7] Increased retention of water is a normal, physiologic alteration of pregnancy, which is under the influence of ovarian, placental, and steroid hormones. At term, an additional 3.0 L of water accumulates subsequent to an increase in maternal blood volume and in the size of the uterus and breasts.[7] The return to baseline of corneal thickness after delivery can be explained by the mobilization and excretion of water at this time.

Although previous reports on the relationship between intraocular pressure and corneal thickness are contradictory, they raise the possibility that changes in corneal thickness also could be related to changes in intraocular pressure. In the presence of well-functioning corneal endothelium, it has been suggested that decreased intraocular pressure is associated with increased corneal thickness.[8] In our study, and in others,[9,10] intraocular pressure was reduced during pregnancy. However, we found no correlation between corneal thickness and intraocular pressure.

Changes in corneal thickness and topography may account for intolerance to contact lens wear experienced by many pregnant women.[1-5] Hence, one may wish to delay fitting new contact lenses until several weeks postpartum,

when corneal thickness has returned to its baseline value.

ACKNOWLEDGMENT

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OPHTHALMIC MINIATURE

When I was in my twenties, I said, I had a job as an 'expert' on modern painting with a well-known firm of art auctioneers. We had sale-rooms in London and New York. I was one of the bright boys. People said I had a great career, if only I would play my cards right. One morning, I woke up blind.

During the course of the day, the sight returned to the left eye, but the right one stayed sluggish and clouded. The eye specialist who examined me said there was nothing wrong organically, and diagnosed the nature of the trouble.

"You've been looking too closely at pictures," he said. "Why don't you swap them for some long horizons?"

I went to Africa, to the Sudan. My eyes had recovered by the time I reached the airport.

Bruce Chatwin, *The Songlines*
New York, Viking, 1987, p. 16

Enlargement of the Blind Spot Caused by Papilledema

James J. Corbett, M.D., Daniel M. Jacobson, M.D., Richard C. Mauer, M.D., and H. Stanley Thompson, M.D.

Blind spot enlargement in papilledema has been attributed to either mechanical disruption of the integrity of the peripapillary percipient elements by the swollen optic disk or to the Stiles-Crawford effect. We investigated the possibility that blind spot enlargement in papilledema is caused, at least in part, by a refractive scotoma due to peripapillary hyperopia. We reduced the enlarged blind spot in a patient with focal peripapillary hyperopia, without papilledema, to near normal size by using progressively stronger plus lenses. Similarly, with the addition of plus sphere, we reduced the size of the blind spot in five of six patients with papilledema, but in none of our normal subjects.

Enlargement of the blind spot has been the visual field hallmark of papilledema since Knapp's description in 1870.[1] The normal blind spot lies in a zone between 13 and 18.5 degrees temporal to the point of fixation and has dimensions of 5.5 degrees in horizontal width and 7.5 degrees in vertical height, when tested with the I_{4e} test object.[2] This is the size of the absolute scotoma, that is, the zone that does not change in size with higher stimulus intensity. Surrounding the absolute scotoma is a narrow amblyopic zone, the relative scotoma, whose size does depend upon the stimulus intensity: the dimmer or smaller the stimulus, the larger the relative scotoma.

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Wilbrand and Saenger[3] related blind spot enlargement in papilledema to lateral retinal displacement and folds in the retina. They also implicated pressure on the circumpapillary retina by the edematous tissue. Retinal displacement would account for an absolute enlargement of the blind spot; however, it does not explain the larger "sloping" relative scotoma that is characteristic of optic disk swelling.[4]

The current explanations offered for the relative scotoma are compression and displacement of the retinal percipient elements by the edematous optic nerve fibers,[3,5] and the Stiles-Crawford effect.[6] The latter phenomenon proposes that the wrinkles and folds in the peripapillary retina cause light to fall obliquely on the photoreceptors, thus making the light a less effective stimulus.

Our observations from the following case report and perimetric investigations in patients with papilledema suggest that the relative scotoma associated with papilledema is predominantly a refractive scotoma resulting from local, peripapillary hyperopia induced by elevation of the retinal percipient elements surrounding the swollen optic disk.

Case Report

At age 27 years, this man had a refractive error of R.E.: -2.50 $+0.75 \times 172$ and LE.: -2.50 $+0.50 \times 180$. Visual acuity was 20/15 in both eyes. At age 34 years, eight months before our examination, he developed intermittent blurred vision in his left eye. The episodes lasted about 30 minutes, occurred three or four times daily, were not associated with any identifiable precipitating factor, and blurred his vision at distance and near to the same degree.

On examination cycloplegic refraction was R.E.: -1.75 $+0.75 \times 170$ (20/15) and L.E.: $+0.75$ $+0.25 \times 40$ (20/15). His near visual acuity equivalent was 20/20 in each eye. Photostress recovery times were normal in each eye. He correctly identified 14 of 14 pseudoisochro-

matic plates in each eye. Contrast sensitivity and critical flicker fusion (a test of visual-temporal resolution) were normal in both eyes. He had no relative afferent pupillary defect. Slit-lamp examination was normal. Intraocular pressure was R.E.: 17 mm Hg and L.E.: 15 mm Hg. Ophthalmoscopy showed retinal folds and patchy elevation of the peripapillary retina in the left eye (Fig. 1). The optic disks were not elevated.

Fluorescein angiography confirmed the chorioretinal folds in the left eye and did not show any leakage of dye in the peripapillary region or macula. Orbital echography disclosed moderate bilateral distention of the arachnoidal sheaths, axial eye lengths of 25.3 mm in the right eye and 23.9 mm in the left eye, and no orbital mass. Results of computed tomography of the orbits were normal. Cerebrospinal fluid analysis showed an opening pressure of 210 mm H_2O, one erythrocyte, two leukocytes, a protein level of 0.41 g/l, a glucose level of 3.4 mmol/l, and normal cytologic findings.

Initial Goldmann visual fields, performed without refractive correction, showed an enlarged blind spot in the left eye using the I_{2e} target and normal-sized blind spot in the left eye using the I_{3e} target (Fig. 2). The perimetrist, unaware of the patient's refractive error, then found a normal-sized blind spot with the I_{2e} target using a +2.00 lens. The patient was reexamined by another perimetrist who was also unaware of his refractive error and of the previous perimetrist's findings. She was instructed only to plot the blind spot using the I_{2e} target without correction, with a +1.00 lens and a +2.00 lens. The size of the blind spot became progressively smaller with increasing plus lenses (Fig. 3).

Patients and Methods

We studied the size of the blind spot in five patients with papilledema caused by pseudotumor cerebri and in one patient with disk swelling caused by posterior uveitis. All were tested with kinetic perimetry using their optimal refraction. The blind spot was plotted using the I_{4e} test object. Successive examinations of the blind spot were performed using additional plus sphere until the blind spot no longer changed in size. Patients were also tested in a reverse manner, starting with a high plus lens and gradually reducing the spherical power on successive examinations. Ten normal subjects also underwent similar examinations to measure the effect of additional plus lenses on the size and position of the blind spot.

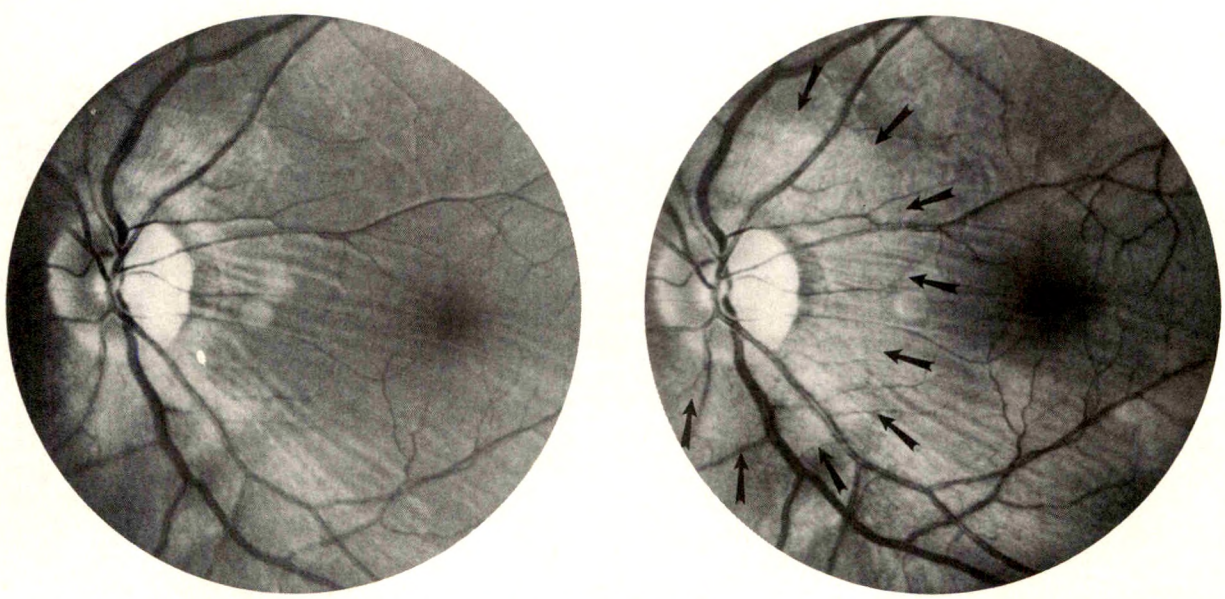


Fig. 1 (Corbett and associates). Stereophotographic pair of the posterior pole of the left eye showing retinal folds extending temporally from the optic disk. The optic disk is not swollen, but the peripapillary retina is elevated (arrows). For optimal stereoscopic viewing, either a stereoviewer or suitable convex spheres mounted in a trial frame can be used.

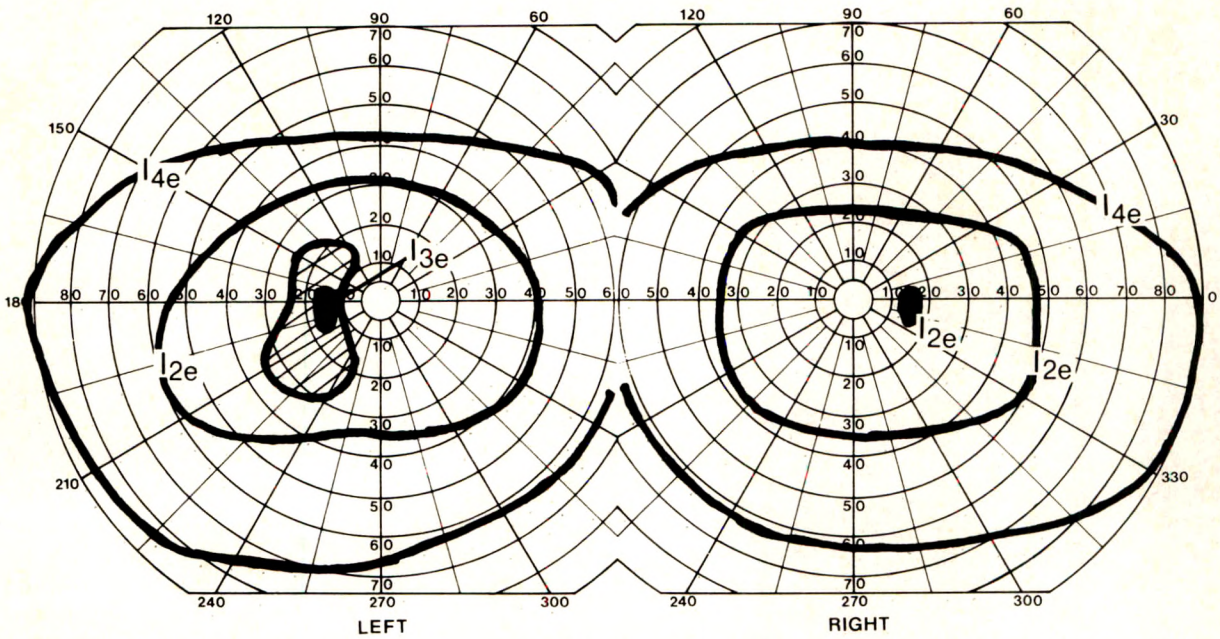


Fig. 2 (Corbett and associates). Goldmann visual field without refractive correction showing large relative scotoma around the blind spot in the left eye using the I_{2e} target but a near normal size blind spot using the I_{3e} target. When a +2.00 diopter sphere was used (not shown), the size of the blind spot using the I_{2e} target was just slightly larger than that shown for the I_{3e} target.

Results

The blind spot in each patient with papilledema, except one, became progressively smaller as more plus sphere was added to the refraction. The amount of plus lens needed to shrink the blind spot maximally ranged from 4 to 6 diopters; the larger the blind spot, the more plus lens needed. We reduced the blind spot to almost normal size in most patients. If more plus lens was added at this point, the blind spot began to enlarge once again. We presume that the focal point lay above the level of the retinal receptors, which formed a blur circle. Minus lens added to the initial refraction predictably enlarged the blind spot.

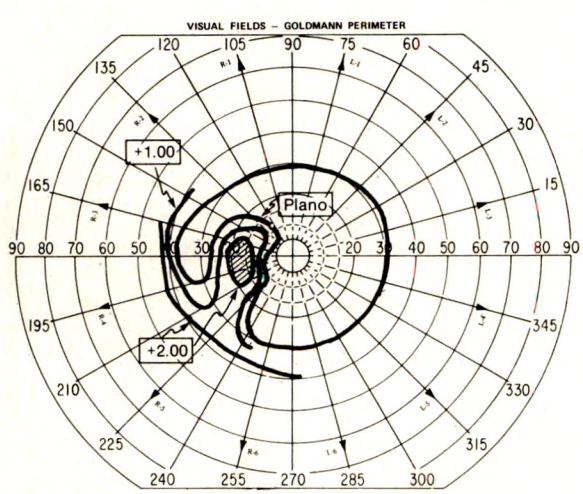


Fig. 3 (Corbett and associates). Goldmann visual field of the left eye. The size of the relative scotoma surrounding the blind spot became progressively smaller by using progressively stronger plus sphere.

Not all blind spots contracted uniformly with addition of plus lens. In several patients with mild papilledema, the portion of the blind spot corresponding to nasal retina was all that constricted. This probably reflects differences in elevation of peripapillary retina as well as lateral folding and displacement. The superior, inferior, and nasal portions of the disk tend to swell early in papilledema and the temporal portions elevate later.[7] The commonly seen temporal indentation in the enlarged blind spot probably reflects this differential swelling.

Although the size and shape of the blind spot did not change in normal subjects, in several subjects it was slightly nasally displaced and the superior pole tilted toward the macula. This curious finding was seen only in a few of the controls and may have been a prismatic effect.

Discussion

The observations in our reported case demonstrate that the relative scotoma surrounding the blind spot can be enlarged simply on a refractive basis from peripapillary hyperopia alone, independent of elevation of the optic disk. The cause of this patient's acquired hyperopia with choroidal folds remains unexplained. Dailey and colleagues[8] have also demonstrated a refractive scotoma in some of their patients with idiopathic acquired hyperopia with choroidal folds. Frisén[9] used the Stiles-Crawford effect to explain the enlarged blind spot in his patient with chorioretinal folds from papilledema. In support of our proposed mechanism for blind spot enlargement in papilledema, we observed that the enlargement can be reduced to almost normal size by using plus lenses in patients with optic disk edema.

Using kinetic perimetry, the size of the relative scotoma surrounding the blind spot is dependent on several variables, including the size and brightness of the target, the direction of the target movement (centrifugal or centripetal), the speed of target movement, the patient's reaction time, and the perimetrist's accuracy in judging the position on the field diagram corresponding to the patient's response. This last element may also be affected by examiner expectation. Because of the many factors influencing the plotting of a small portion of the visual field, our findings may be subject to an unacceptable amount of variation. However, the first two variables mentioned above were constant and all attempts were made to maintain a standard speed of target movement. Although the patient's and perimetrist's reaction times probably varied to some extent, we do not believe that this factor was overwhelmingly important, since our results consistently demonstrated an inverse relationship between size of the blind spot and amount of plus lens used in multiple subjects and examiners.

Hyperopia has been reported in patients with choroidal folds caused by intraconal orbital tumors.[10] Havener and McReynolds[11] found that a refractive error can produce a central refractive scotoma, the intensity of which depends on the degree of ametropia. This scotoma disappears with refractive correction to emmetropia. The classic refractive scotoma is that caused by ectasia of the inferior nasal fundus, or a tilted disk. This staphylomatous defect requires minus lens to correct the superior temporal field defect it produces.[12] Thus, any refractive error in the retina, properly tested, will be perceived by the patient as if there were a scotoma.

In addition to lateral displacement of the retina by the swollen disk tissue, the Stiles-Crawford effect has been invoked as a possible cause of enlarged blind spot in papilledema. In the Stiles-Crawford effect, the apparent brightness of an object decreases as its incidence angle from the longitudinal axis of the photoreceptor increases.[6] If light rays striking a laterally folded retina caused the relative enlargement, then the addition of plus lens should have no effect on the size of the blind spot since refractive correction would not affect the efficiency with which the receptors detected a signal.

In 1930, Reese[13] suggested that in papilledema, detachment of the peripapillary retina may explain the excessively large blind spot. Later, Samuels[14] documented eight cases in which the retina had a narrow slit-like detachment extending some distance from the disk under the surrounding retina. In a detailed pathologic study of 50 globes with papilledema, Samuels pointed out that "from the pictures in most textbooks, it would appear that the lateral distention of the papilla merely pushes the retina aside." According to his studies, however, "such simple pushing aside of the retina was far from the rule. It was, in fact, only found in one-third of the cases."[14] In those cases in which a greatly enlarged papilla exerted an elevating action on the retina, a space was often insinuated between the retina and pigment epithelium, lifting the retina. This space was a proliferation of the intermediary tissue of Kuhnt, a collar of neuroglia normally interposed between the nonmedullated nerve fibers and the neuroepithelium of the retina.

By virtue of its barrier property, this intermediary tissue prevents diffusion from the prelaminar region into the peripapillary retina and subretinal space.[15] Because cells in this tissue lack tight junctions, it is assumed to be a functional barrier.[16] The intermediary tissue of Kuhnt is frequently disrupted by papilledema, allowing horseradish peroxidase from the optic nerve head to move into the peripapillary subretinal space.[15] Furthermore, using fluorescein angiography, late, deep hyperfluorescence extends into this same peripapillary region in experimental papilledema. With more marked optic disk edema, fluorescence is not only more intense but involves a larger area.[17]

The source of the subretinal fluid is not known for certain; it could originate in the peripapillary choroid, the cerebrospinal fluid, or the vitreous. Tso, Shi, and McLean[18] showed a breakdown of the blood-brain barrier at the disk in monkeys with experimental disk edema. Horseradish peroxidase has been traced from the choriocapillaries along Bruch's membrane and through the border tissue of Elschnig,[18] thereby implicating the peripapillary choroid as the source of the fluid. However, fluorescein injected into the cisterna magna in normal rhesus monkeys is also found in the peripapillary retina upon enucleation.[17] This suggests that cerebrospinal fluid can move through the barrier to the subretinal space. Intravitreal injection of horseradish peroxidase results in free diffusion through the internal limiting membrane into the intercellular spaces of the optic nerve parenchyma in normal monkeys, suggesting that the vitreous may be the site of origin of the fluid.[19]

The long-held belief that enlargement of the blind spot in papilledema is a result of simple mechanical displacement and folding of the retina fails to explain our visual field observations. In addition to mechanical factors, another mechanism, refractive scotoma, accounts in large measure for the enlarged blind spot in disk edema. Peripapillary subretinal fluid collection elevating the retina from the retinal pigment epithelium seems a sufficient reason for this local hyperopia.

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Recombinant Tissue Plasminogen Activator to Lyse Experimentally Induced Retinal Arterial Thrombi

Andrew K. Vine, M.D., Paul T. Maguire, M.D., Csaba Martonyi, and Marilyn C. Kincaid, M.D.

We evaluated the efficacy of intravenously administered recombinant tissue plasminogen activator to lyse laser-induced arterial thrombi in the stroke-prone, spontaneously hypertensive rat model. The arterial thrombi were confirmed histologically, and assessed by color photographs and fluorescein angiography before and after intravenous tissue plasminogen activator or saline therapy. Experimental animals received tissue plasminogen activator (1 mg/kg of body weight) given intravenously over one hour, and control animals received similar volumes of normal saline. Tissue plasminogen activator was effective in lysing experimental retinal arterial thrombi.

CENTRAL RETINAL arterial occlusions typically result in profound visual loss. Despite numerous proposed therapies, dissolution of the embolus or thrombus is typically unsuccessful, resulting in permanent visual loss. Recombinant technology has recently resulted in the production of a clot-specific fibrinolytic agent, recombinant tissue plasminogen activator (rt-PA), which is presently being used to lyse acute thrombi in coronary arteries. We studied the efficacy of rt-PA to lyse experimentally induced retinal arterial thrombi in the stroke-prone, spontaneously hypertensive rat.

Material and Methods

Eighteen 300-g, male, stroke-prone, spontaneously hypertensive rats were anesthetized with a mixture of xylazine (13 mg/kg of body weight) and ketamine (87 mg/kg of body weight) given intramuscularly. Both eyes were dilated with one drop each of 1% tropicamide and 2.5% phenylephrine. The animal was then supported in front of the slit-lamp delivery system of an argon laser. A small Goldmann lens with hydroxylethylcellulose gel was placed over one eye. Using the slit-lamp biomicroscope, a small section of a retinal arteriole close to the disk was photocoagulated with the blue-green argon laser. The laser settings were 50-μm spot size, 0.1- to 0.2-second exposure, and 100 to 200 mW. Treatment of the arteriole with laser therapy under high magnification initially produced immediate constriction and marked slowing of the arteriole blood flow, so that individual red blood cells could be visualized passing through the treated segment. With further therapy, the treated segment typically occluded, resulting in a stagnant column of dark blood distal to the occlusion.

To maintain corneal hydration, the eyes were covered with absorable gelatin sponge patches that had been saturated with balanced salt solution. One hour after the vessel had been occluded, color photographs and a fluorescein angiogram (0.15 ml/kg of body weight of 2.5% sodium fluorescein) were done to confirm that the vessel remained closed.

Experimental animals received intravenous rt-PA (1 mg/kg of body weight) given over one hour via a tail vein. A solution of rt-PA in normal saline was made to a concentration of 0.122 mg/ml. Of the total rt-PA dosage (1 mg/kg of body weight), 21% was given as an initial intravenous bolus in 0.5 ml of normal saline. The remaining rt-PA was given in 0.15 ml of infusion every five minutes over one hour (12 injections). Control animals received an intravenous bolus and similar repetitive infusions of normal saline.

On completion of the infusion, color photographs and a fluorescein angiogram (0.3 ml/kg of body weight of 2.5% sodium fluorescein)

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were repeated to determine the patency of the vessel. The higher dosage of fluorescein for the second angiogram was required because of the residual background fluorescence from the initial angiogram.

In two control animals, the eyes were subsequently removed for histologic examination of the vessel after completion of the second fluorescein angiogram.

Results

Histopathologic examination of retinal arterioles that had been treated with laser therapy confirmed the presence of a confluent intraluminal thrombus, with considerable damage to the vessel wall and surrounding tissue (Fig. 1).

Four eyes developed significant vitreous hemorrhages during laser photocoagulation and were excluded from the series. In one eye, the initial fluorescein angiogram showed the vessel was patent and this eye was also excluded. Twelve rats showed complete occlusion of the treated arterioles on the initial fluorescein angiogram. Six of these rats received intravenous rt-PA and six received intravenous normal saline. The range of number of laser applications was 24 to 147 (median, 44) for experimental rats and 22 to 186 (median, 55) for control rats. The mean power settings for experimental and control arteriolar occlusion were 183 and 180 mW, respectively.

In the control animals, the second fluorescein angiogram after the intravenous infusion of normal saline showed complete occlusion of the treated vessel in all six rats (Fig. 2). In the experimental group, the second fluorescein angiogram after the intravenous infusion of rt-PA showed lysis of the clot and patency of the arteriole in four of the six animals (Fig. 3). These results are statistically significant by Fisher's exact test ($P = .021$).

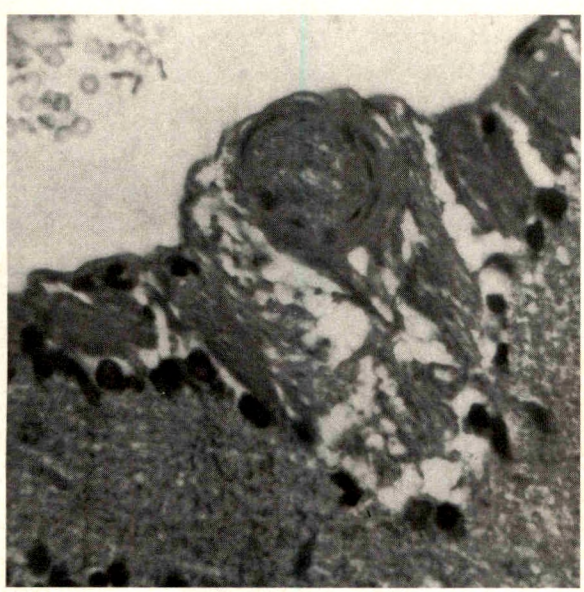


Fig. 1 (Vine and associates). Photomicrograph of cross section of rat retinal arteriole after treatment with argon photocoagulation shows occlusive luminal thrombus, with damage to arterial wall and perivascular tissue. Blood in vitreous occurred during enucleation (hematoxylin and eosin, ×400).

Discussion

Effective therapy for central retinal arterial occlusion and its consequent massive visual loss is presently unavailable. Many patients are first seen by an ophthalmologist after irreversible retinal damage has occurred. The maximum tolerance time of the retina to central retinal arterial occlusion-induced ischemia is unknown. In the monkey model, Hayreh and Weingeist[1] showed that the retina recovered after 97 to 98 minutes of ischemia, but suffered irreparable damage after 105 minutes. A few clinical case reports[2,3] suggest that the human retina may be able to withstand even longer periods of ischemia. Although short, this time period does allow for implementation of emergency therapy if effective therapy were available.

Recombinant tissue plasminogen activator has many advantages over previous fibrinolytic agents. The enzyme's high affinity for fibrin and subsequent binding to plasminogen to form a cyclic ternary complex[4,5] results in a clot-selective fibrinolytic agent that does not induce generalized systemic fibrinogenolysis. With high doses or long infusion times, however, rt-PA can induce a systemic fibrinolytic state.[6] In these circumstances, free plasmin is generated because of the consumption of alpha 2-antiplasmin, and the abundant rt-PA overcomes the low affinity that the activator has for nonfibrin-bound or circulating plasminogen. Studies of rt-PA efficacy in coronary thrombosis have shown that maximal thrombolysis occurs within the first hour.[6]

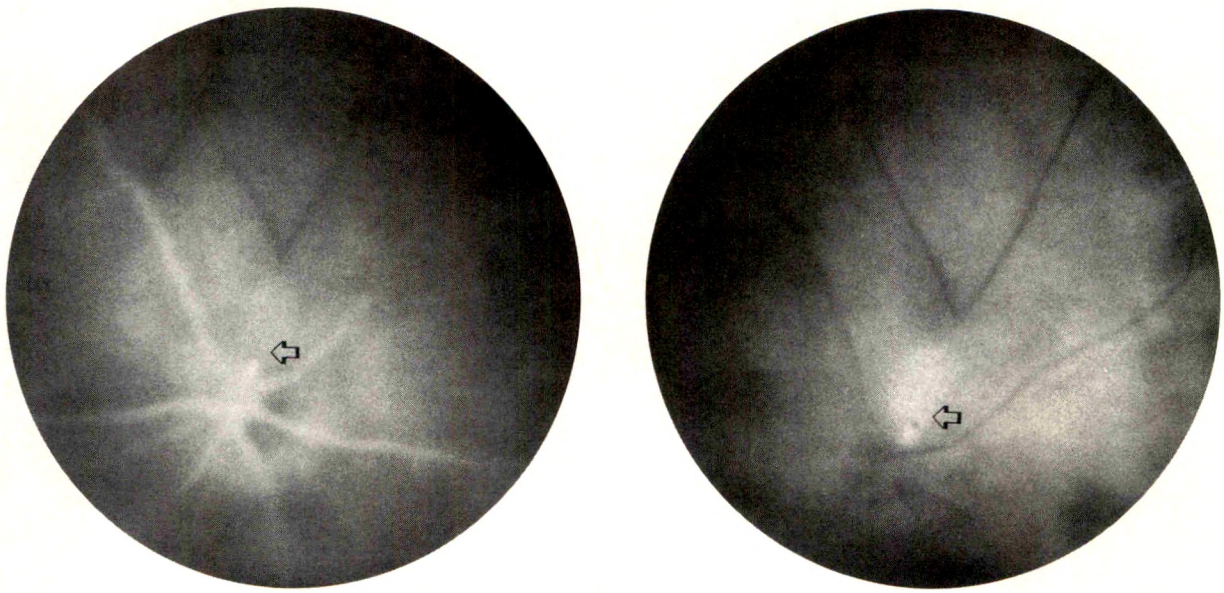


Fig. 2 (Vine and associates). Control rat. Left, Arteriovenous phase of fluorescein angiogram before saline infusion demonstrates occluded arteriole (arrow) at site of previous laser photocoagulation. Right, Arterial phase of fluorescein angiogram after infusion of saline. Arterial occlusion (arrow) is unchanged. Diffuse background hyperfluorescence is caused by retained fluorescein from initial angiograms.

The 67% successful thrombolysis achieved in our experimental retinal arterial occlusions compares favorably to the reported reperfusion rate of 70% to 75% in acute coronary artery thrombosis using a wide range of dosages.[6,7] Failure of thrombolysis may partially reflect the extreme variation of plasma drug levels at mid-infusion, which does not appear to be a function of dosage.[6] Differences between species in rt-PA and possible severe laser damage to the arteriole in some animals may also account for some failures.

The stroke-prone rat,[8] a substrain of the spontaneously hypertensive rat, is a well-established genetic strain of rats in which severe hypertension develops 100% of the time and cerebral hemorrhages develop 80% of the time. A severe degenerative retinal dystrophy[9] may also occur late in the first year of life in these rats. Although the animals showed marked arterial constriction, no other clinical signs of hypertensive retinopathy were present. Despite the small size of the eyes, accurate focal arterial photocoagulation was possible and subsequent reasonable fluorescein angiography was feasible. The number of laser burns required to close each arteriole was variable and depended on the quality of the focusing media. Despite rigorous attempts to maintain corneal hydration, corneal haze or distortion of the cornea by the contact lens would result in distortion of the laser beam and inefficient delivery of the laser pulse to the selected arteriole. The clarity of the ocular media during the actual laser therapy was the main variable that accounted for the wide range in number of laser burns required to induce a thrombus. Other factors may also be involved, including the degree of hypertension, vessel caliber, and the severity of the underlying vessel disease.

The occlusive thrombus and generalized hypertensive arterial constriction simulate two features that are present in some clinical retinal arterial occlusions. Laser-induced damage to the arterial wall and perivascular tissue and the nonembolic nature of the thrombus are two nonphysiologic features of our model. Most clinical retinal arteriole occlusions are embolic in nature and the embolized material may not be amenable to lysis with rt-PA. Although the results are statistically significant, the number of involved animals is small. Our study shows that rt-PA can reperfuse occluded retinal arterioles, but we cannot provide any data on the

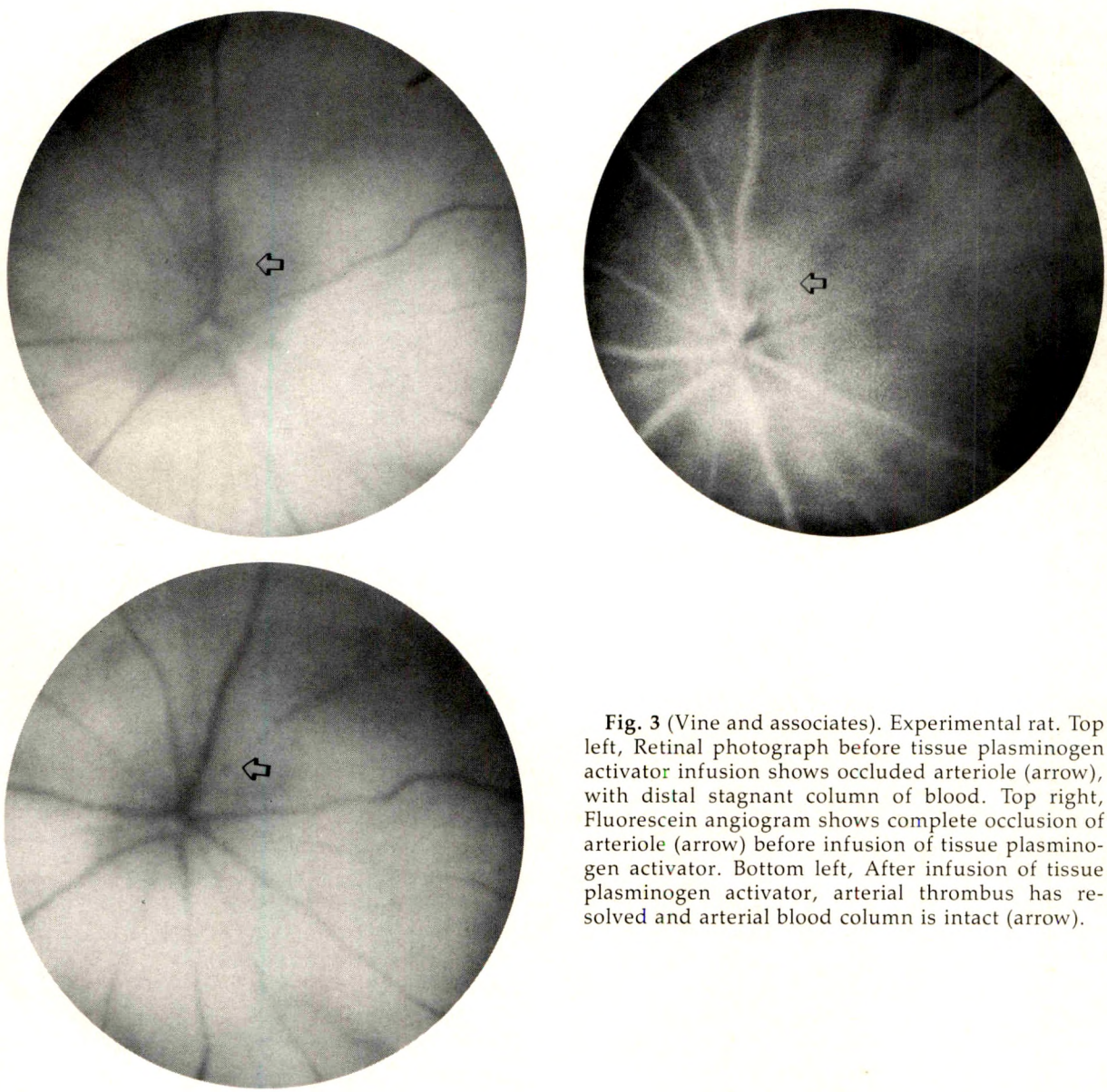


Fig. 3 (Vine and associates). Experimental rat. Top left, Retinal photograph before tissue plasminogen activator infusion shows occluded arteriole (arrow), with distal stagnant column of blood. Top right, Fluorescein angiogram shows complete occlusion of arteriole (arrow) before infusion of tissue plasminogen activator. Bottom left, After infusion of tissue plasminogen activator, arterial thrombus has resolved and arterial blood column is intact (arrow).

maintenance of perfusion beyond one hour. Increasing corneal haze and retained fluorescein within the retina and choroid made later fluorescein angiograms difficult. Further studies are needed to address these questions.

ACKNOWLEDGMENT

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OPHTHALMIC MINIATURE

I'm not trying to prove anything, by the way. I'm a scientist and I know what constitutes proof. But the reason I call myself by my childhood name is to remind myself that a scientist must also be absolutely like a child. If he sees a thing, he must say that he sees it, whether it was what he thought he was going to see or not. See first, think later, then test. But always see first. Otherwise you will only see what you were expecting. Most scientists forget that. I'll show you something to demonstrate that later. So, the other reason I call myself Wonko the Sane is so that people will think I am a fool. That allows me to say what I see when I see it. You can't possibly be a scientist if you mind people thinking that you're a fool.

Douglas Adams, *So Long, And Thanks For All The Fish*
New York, Pocket Books, 1984, p. 165

Unusual Central Chorioretinitis as the First Manifestation of Early Secondary Syphilis

Eduardo Cunha de Souza, M.D., Alex E. Jalkh, M.D., Clement L. Trempe, M.D., Sergio Cunha, M.D., and Charles L. Schepens, M.D.

Three young, otherwise healthy patients had a similar picture of unilateral central chorioretinitis associated with severe visual loss. Fluorescein angiography disclosed diffuse leakage under the neurosensory retina in the posteror pole, associated with multifocal areas of staining along the retinal vessels. Systemic examination showed a positive fluorescent treponemal antibody absorption test and a sharp increase in VDRL titers, indicative of active secondary syphilis. The patients responded dramatically to penicillin treatment, with visual recovery and resolution of the fundus lesions.

ALTHOUGH THERE ARE no pathognomonic signs of acquired ocular syphilis, it is not uncommon for an ophthalmologist to detect the disease in patients who have only ocular manifestations. *Treponema pallidum* was at one time considered a frequent cause of uveal disease and was held responsible for some of the most dramatic types of intraocular inflammation. The most common ocular manifestations of syphilis are uveitis, diffuse chorioretinitis, and vasculitis.[1] We describe herein three unusual cases showing a similar and peculiar type of central chorioretinitis as a first manifestation of early secondary syphilis.

Case Reports

Case 1

A 28-year-old woman had a recent history of severe decrease in visual acuity in the right eye. Her medical and family history were unremarkable. Best corrected visual acuity was R.E.: hand motions and L.E.: 20/20. Slit-lamp examination showed 1+ cells and flare in the anterior chamber and anterior vitreous of the right eye. Ophthalmoscopy and biomicroscopy showed cells in the posterior vitreous and a detached neurosensory retina in the posterior pole associated with a rim of yellow subretinal exudates (Fig. 1, top left). Findings in the left eye were normal. Fluorescein angiography of the right eye showed early irregular hyperfluorescence temporal to the fovea (Fig. 1, top right), with leakage under the neurosensory retina in the posterior pole and multifocal areas of perivascular staining in the late transit stage (Fig. 1, bottom left). The optic disk was normal. Physical examination was unremarkable. The laboratory tests showed a positive fluorescent treponemal antibody absorption test, a positive VDRL at 1:32 dilution, and a low serum complement.

One week later, the patient began complaining of malaise, fever, and symptoms of arthritis in her left wrist. Results of the VDRL were positive at 1:512 dilution, and the serum complement was normal. The cerebrospinal fluid was normal. She was treated with 2.4 million units of penicillin G benzathine intramuscularly as an initial dose and then 1.2 million units daily for eight days. Over the next several weeks, visual acuity in the right eye improved to 20/30. Three months later the anterior segment was normal, and ophthalmoscopy demonstrated mild pigmentary changes in the macula (Fig. 1, bottom right).

Case 2

A 23-year-old, sexually active, homosexual man complained of recent loss of vision in his right eye. The medical and family history were unremarkable. Best corrected visual acuity was

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From the Eye Research Institute of Retina Foundation and Retina Associates, Boston, Massachusetts.

Reprint requests to Library, Eye Research Institute, 20 Staniford St., Boston, MA 02114.

R.E.: hand motions and L.E.: 20/20. Slit-lamp examination of the right eye disclosed 1+ cells and flare in the anterior chamber and anterior vitreous. Ophthalmoscopy and biomicroscopy showed cells in the posterior vitreous and an elevated, yellow lesion under the neurosensory retina in the macula (Fig. 2). The left eye showed no abnormalities. Fluorescein angiography of the right eye demonstrated leakage under the neurosensory retinal elevation (Fig. 3) and multifocal areas of perivascular staining in the posterior pole (Fig. 4). The optic disk was normal. Results of systemic examination were unremarkable except for a positive fluorescent treponemal antibody absorption test and a weakly positive VDRL (1:16). The following week, the VDRL became strongly positive (1:256). The cerebrospinal fluid was normal. The patient was treated with 2.4 million units of penicillin G benzathine intramuscularly as an initial dose and then 1.2 million units daily for eight days. Two weeks after treatment, the posterior fundus was normal and the visual acuity in the right eye had improved to 20/20.

Case 3

A 29-year-old man was examined because of blurred vision in the right eye for two days. Visual acuity was R.E.: counting fingers and L.E.: 20/20. The left eye was normal. Slit-lamp examination of the right eye showed 1+ cells and flare in the anterior chamber and anterior vitreous. Indirect ophthalmoscopy disclosed a serous elevation of the neurosensory retina in the macula, associated with a gray ring of subretinal exudation (Fig. 5). Fluorescein angiography showed leakage under the neurosensory retinal detachment associated with perivascular staining in the posterior pole. The optic disk was normal.

Results of a systemic examination were negative except for a positive fluorescent treponemal antibody absorption test and a positive VDRL at 1:32 dilution. One week later the VDRL was positive at 1:256 dilution. The cerebrospinal fluid was normal. The patient was treated with 2.4 million units of penicillin G benzathine intramuscularly as an initial dose and then 1.2 million units daily for eight days. Vision started to improve three days after initiation of therapy. Three weeks later visual acuity was 20/20 in the right eye and results of an ocular examination were unremarkable.

Discussion

Syphilis is a sexually transmitted systemic infection. The incubation period averages three weeks, and it has three clinical stages. The primary stage is characterized by a chancre and regional lymphadenopathy. The secondary stage shows mucocutaneous and multisystem involvement. Between 20% and 25% of untreated patients show one or more relapses within two to four years, often manifested by anogenital and oral lesions.[2] If these lesions heal spontaneously, a latent, asymptomatic period follows. About 25% of the cases progress, after a period of five to 30 years, to the tertiary or late stage, with gummata, cardiovascular syphilis (aortitis), or neurosyphilis (tabes dorsalis and general paresis).[2-4]

The importance of syphilis as a cause of ocular disease has been appreciated since 1858.[5] In 1931 Moore[6] reported that 4.6% of patients with secondary syphilis had uveitis, and up to 9.3% of patients with recurrent secondary syphilis had uveitis. In early acquired syphilis, 73.3% of the cases with ocular manifestations have iritis. Iritis develops in about 4% of all patients with secondary syphilis, but retinitis, chorioretinitis, and neuroretinitis have been observed rarely.[1,5,7]

The most common manifestation of acquired syphilis in the posterior segment of the eye is choroiditis or chorioretinitis, since the retina is almost invariably affected in association with the choroid. Two types of syphilitic chorioretinitis have been described: a disseminated type that appears typically in the late secondary stage of the disease, and a rarer, localized type that occurs later in the course of the disease. The disseminated type is usually bilateral, showing multiple gray-yellow, inflammatory, chorioretinal lesions associated with vitritis. The retina may exhibit vasculitis and edema. This is the commonest type of posterior uveitis in acquired syphilis. The localized type can affect the region of the disk (juxtapapillary choroiditis) or the macula (central choroiditis). It is usually bilateral with a tendency to recur, and it can cause permanent visual damage.

Accurate diagnosis of syphilis is based on both the clinical features and the serologic test results. The latter tests are of two types: for nonspecific antibodies (VDRL), and for specific antitreponemal antibodies (fluorescent treponemal antibody absorption). In primary syphi-

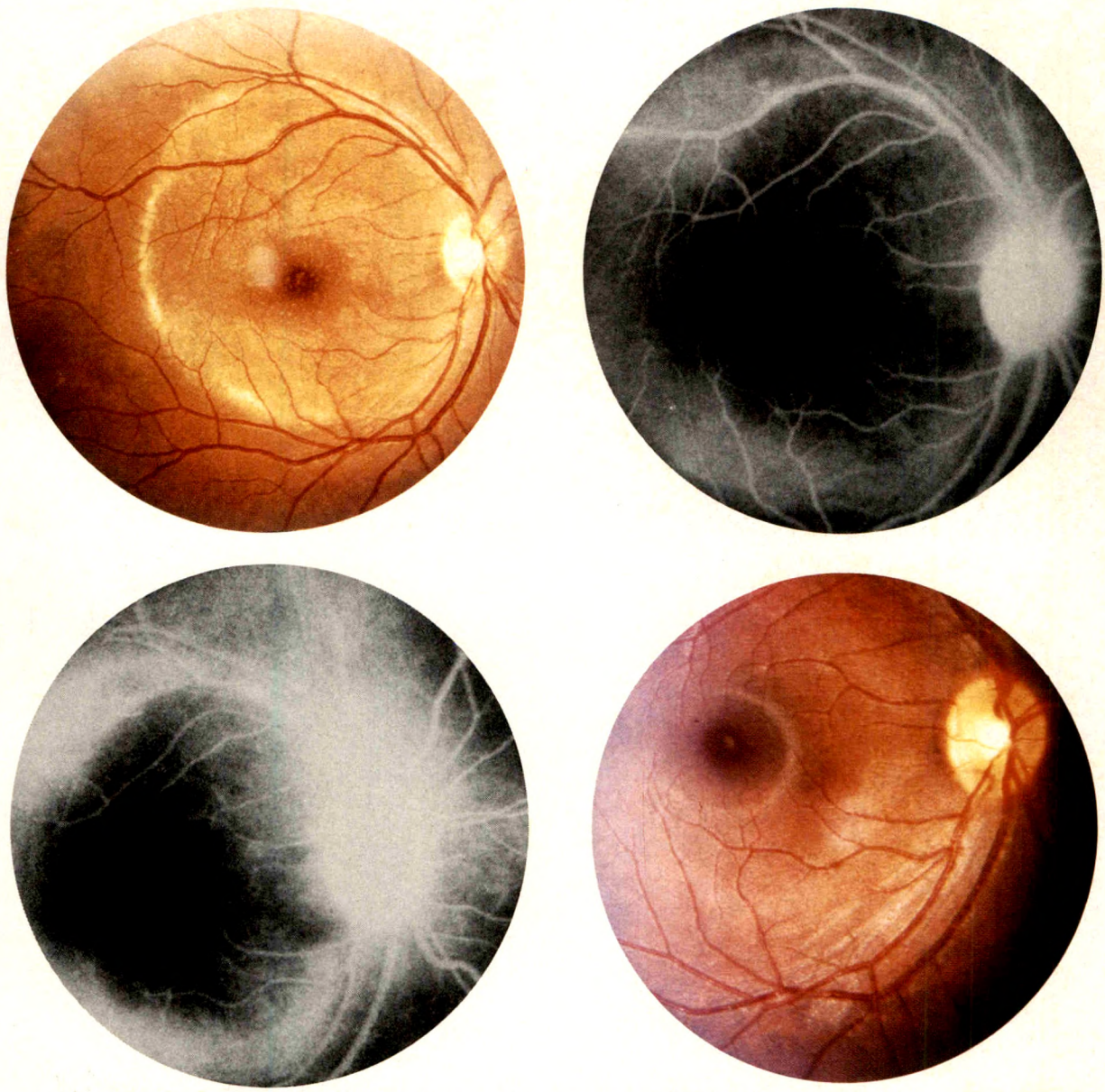


Fig. 1 (de Souza and associates). Case 1. Top left, Fundus photograph showing rim of subretinal exudates along edge of shallowly detached neurosensory retina in posterior pole. Top right, Early transit fluorescein angiogram showing irregular hyperfluorescence temporal to the fovea. Bottom left, Late transit fluorescein angiogram, showing marked leakage under neurosensory retina associated with perivascular staining. Bottom right, Fundus photograph three months after penicillin treatment, showing mild pigmentary changes in the macula.

lis,[2] the latter becomes positive earlier than the VDRL. In secondary syphilis, the serologic tests are usually uniformly positive, 10% to 30% of patients have pleocytosis in the cerebrospinal fluid, and fewer than 1% have symptomatic meningitis.[2,3] A reactive VDRL test in the cerebrospinal fluid is considered indicative of central nervous system infection.[2,3] The latent stage can be detected only by abnormal serologic test results. In tertiary syphilis, the fluorescent treponemal antibody absorption test is usually positive, but the VDRL may be nega-

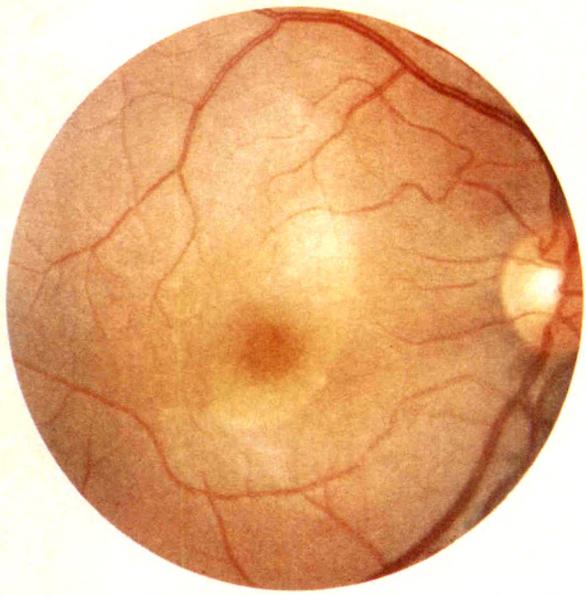


Fig. 2 (de Souza and associates). Case 2. Fundus photograph showing yellow retinal elevation in the macula.

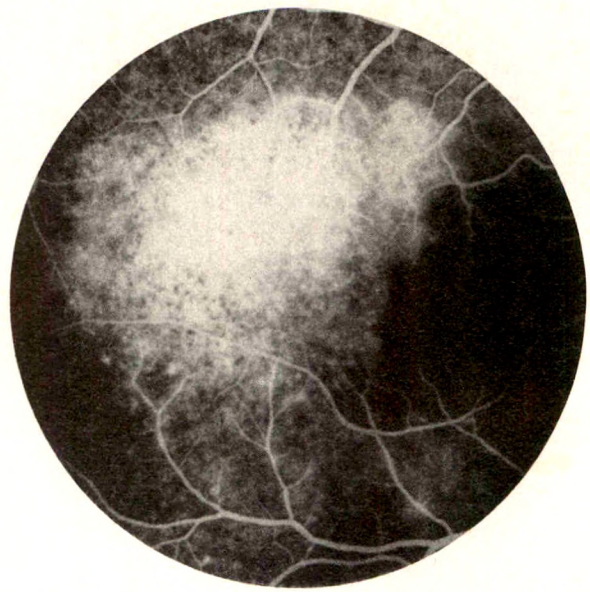


Fig. 3 (de Souza and associates). Case 2. Early fluorescein angiogram, showing leakage from the choroid under the neurosensory retina.

tive. The VDRL is negative in nearly one third of patients with primary or late syphilis.[2-4]

Our three patients had markedly impaired vision because of posterior pole involvement as the first manifestation of acquired syphilis. All three patients were young and systemically asymptomatic. The clinical and angiographic findings are suggestive of primary choroidal involvement, which caused a sensory retinal detachment and was associated with retinal

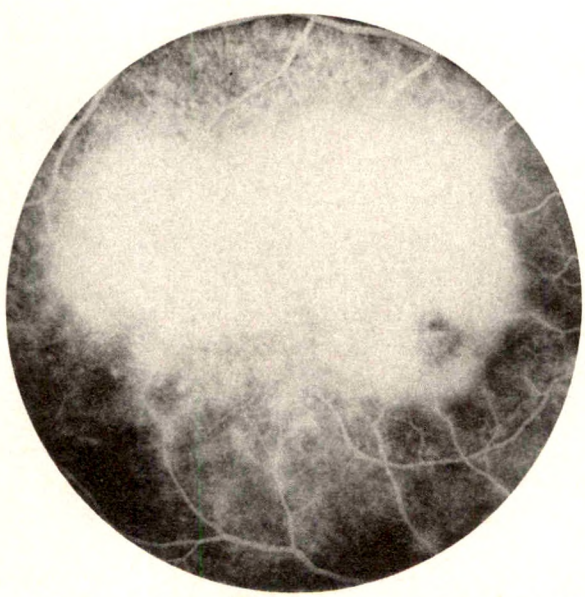


Fig. 4 (de Souza and associates). Case 2. Late fluorescein angiogram, showing marked leakage under the neurosensory retina associated with perivascular staining.

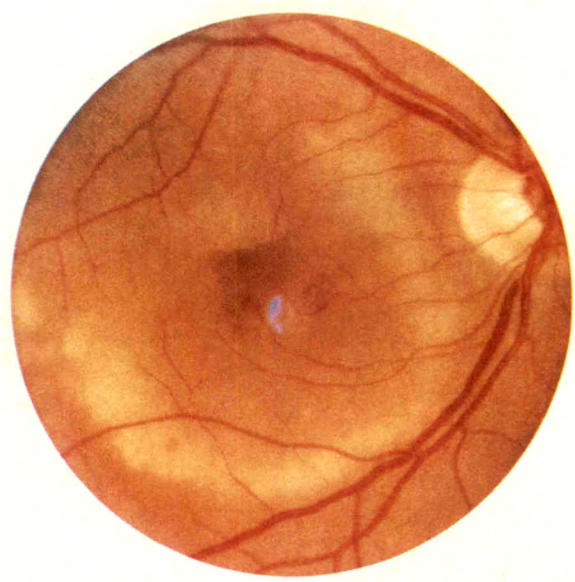


Fig. 5 (de Souza and associates). Case 3. Fundus photograph showing shallow elevation of neurosensory retina associated with a gray ring of subretinal exudative fluid around the posterior pole.

vasculitis. The latter manifestation has been reported by several authors.[8-12] In our cases, the differential diagnosis included central serous chorioretinopathy, occult subretinal neovascularization, optic pit, and other forms of chorioretinitis such as toxoplasmosis, toxocariasis, and tuberculosis. The diagnosis of optic pit can easily be ruled out because of its typical characteristics seen on biomicroscopy and fluorescein angiography. Occult subretinal neovascularization usually is not associated with diffuse subretinal leakage and perivascular staining. Central serous chorioretinopathy usually has clear subretinal fluid, shows focal areas of subretinal leakage and no perivascular staining, and is not associated with severe visual loss.

Other forms of chorioretinitis, such as toxoplasmosis, toxocariasis, and tuberculosis, could give a clinical picture similar to our cases, but the positive serologic results for syphilis ruled out these entities.

The diagnosis of syphilis was strongly suggested by the positive fluorescent treponemal antibody absorption test, initially associated with positive low titers of VDRL. These patients had undetected or asymptomatic primary syphilis. Primary sites, such as the cervix and labia in women and the anal canal[2] in homosexual men, can be overlooked easily. In all three patients, the presence of a positive fluorescent treponemal antibody absorption test associated with increasing titers of VDRL and normal cerebrospinal fluid were indicative of early active secondary syphilis.[2-4,13]

The presence of soluble immune complexes in syphilis has been well documented,[14,15] and the central chorioretinal lesions in our cases may have resulted from the deposition of soluble immune complexes at the level of the retinal pigment epithelium-choriocapillaris and possibly of the retinal vessels. Wozniczko-Orlowska and Milgrom[16] found that sera with low VDRL titers (<1:16) had a high incidence of circulating immune complexes. Once deposited on vessel walls, these may fix complement and initiate an inflammatory process.[4,17] This might explain the low serum complement values detected early in Patient 1. Unfortunately, we did not test all three patients for serum complement or immune complexes. An identical mechanism is responsible for some cases of glomerulonephritis associated with early secondary syphilis.[18-20] However, only a small percentage of patients develop circulating immune complexes during early acquired syphilis,[19] and why such depositions occur in selected sites is unknown.

Our cases represent unusual manifestations of ocular syphilis, which to our knowledge have not yet been well documented, although a few cases have been described.[21,22] The central chorioretinitis may have been induced by an immune complex mechanism. The appropriate treatment of syphilis resulted in full recovery of vision and complete resolution of the fundus lesions in all three patients. Our observations demonstrate the importance of recognizing this potentially disabling and specifically treatable disease, despite its uncommon clinical findings.

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OPHTHALMIC MINIATURE

She felt the first foreboding. The little fear that always came to her before delicate eye surgery. For her the eye was beautiful, a true window to the soul. It made a perfect whole with its dense white sclera, the colored curtain of the iris, the lens like a pearl in its elastic capsule, the humors that provided shape and firmness and the pigmented choroid coat which darkened the inner chamber of the eye and gave it mystery. It hurt her to see it diseased or damaged, and she never began an operation without wanting with all her heart and mind to restore to it a clear unblemished light.

Ronald Hardy, *Rivers of Darkness*
New York, G. P. Putnam's Sons, 1979, p. 164

Anterior Proliferative Vitreoretinopathy

Hilel Lewis, M.D., and Thomas M. Aaberg, M.D.

During a four-year period, 53 of 92 eyes (58%) undergoing vitreoretinal surgery for a retinal detachment with proliferative vitreoretinopathy demonstrated anterior proliferative vitreoretinopathy. We classified anterior proliferative vitreoretinopathy according to tractional direction, location, extent, and severity. Initially, the eyes were treated with a high scleral buckle and laser endophotocoagulation as an adjunct to vitrectomy. Treatment then evolved into a direct approach in which the anterior proliferative tissue was surgically cut or excised. Of the 42 eyes followed up for at least six months, 25 (59%) were totally reattached and 18 (43%) had a visual acuity of 5/200 or better.

PROLIFERATIVE VITREORETINOPATHY,[1] a disorder in which membranes proliferate on the periretinal surfaces after retinal detachment, is the principal cause of failure in rhegmatogenous retinal detachment surgery.[2] Recognition of the different forms of proliferative vitreoretinopathy is necessary to plan the appropriate treatment and improve the anatomic and visual outcome of these severe cases.

Although posterior proliferative vitreoretinopathy is well understood, anterior proliferative vitreoretinopathy is not well described.[3,4] During the last four years we paid particular attention to the vitreoretinal anatomy in the region of the vitreous base in all cases of retinal detachment. Based on the tractional forces at the vitreous base we classified anterior proliferative vitreoretinopathy to guide our surgical approach. Herein we report the prevalence, our surgical technique, and the long-term results in patients with anterior proliferative vitreoretinopathy.

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Material and Methods

Between January 1983 and December 1986, 92 eyes of 90 patients with rhegmatogenous retinal detachment and proliferative vitreoretinopathy underwent vitreoretinal surgery performed by one of us (T.M.A.). We excluded eyes with proliferative vitreoretinopathy caused by penetrating ocular injuries, giant tears, inflammatory disease, vaso-occlusive diseases, diabetic retinopathy, or eyes repaired by scleral buckling without vitrectomy.

Each patient was examined preoperatively and intraoperatively, with particular attention given to the vitreoretinal relationships at the vitreous base. Best corrected visual acuity and intraocular pressure were determined in each patient before and after surgery. The anterior segment, retina, and vitreous were studied with slit-lamp biomicroscopy, gonioscopy, contact lens, and indirect ophthalmoscopy. Posterior proliferative vitreoretinopathy was graded according to the classification adopted by the Retina Society Classification Committee.[1] Anterior proliferative vitreoretinopathy was defined as proliferation anterior to the posterior insertion of the vitreous base and was prospectively graded according to the classification described below. We followed up 74 eyes for six months or longer after surgery.

The anatomic classification of anterior proliferative vitreoretinopathy was based on the extent of anterior displacement of the posterior border of the vitreous base. This anterior displacement extended to the anterior vitreous base insertion (Fig. 1, top left), to the pars plicata (Fig. 1, top right), to the posterior iris surface (Fig. 1, bottom left), or to the pupillary margin (Fig. 1, bottom right).

Three types of tractional forces at the vitreous base were recognized (Table 1). Anteroposterior traction was manifest as anterior dis-

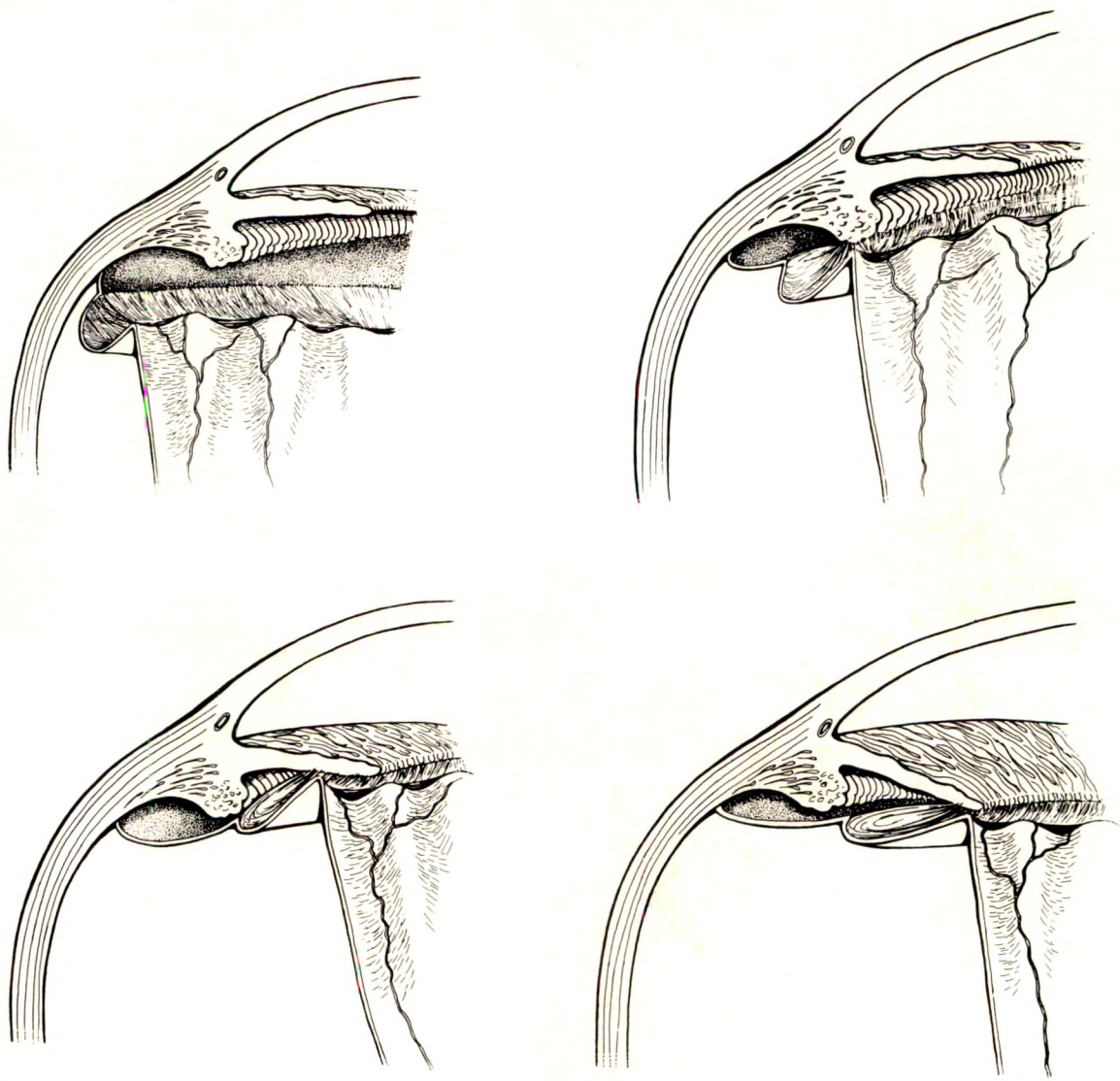


Fig. 1 (Lewis and Aaberg). Anterior proliferative vitreoretinopathy. Top left, Anteroposterior traction with the posterior border of the vitreous base displaced toward its anterior insertion creating a trough or concavity. Top right, Anteroposterior traction with the posterior border to the vitreous base adherent to the pars plicata. Bottom left, Anteroposterior traction with the posterior border of the vitreous base adherent to the posterior iris surface. Note the posterior retraction of the iris. Bottom right, Anteroposterior traction with the posterior border of the vitreous base adherent to the pupillary margin. Note the marked posterior retraction of the iris.

placement of the posterior vitreous base insertion. It is caused by traction from proliferating tissue within the vitreous base and on the anterior vitreous hyaloid surface. This traction is recognized clinically by the presence of a trough at the vitreous base (Fig. 1, top left and right). Posterior retraction of the iris may or may not occur (Fig. 1, bottom left and right), since it is dependent on attachment of proliferative tissue to the posterior iris or ciliary processes.

Anterior circumferential traction is caused by proliferative tissue on the anterior and posterior vitreous surfaces, creating a ring at the vitreous base (Fig. 2). It is recognized clinically by the occurrence of radial retinal folds that

TABLE 1
DIRECTION OF TRACTIONAL FORCES AT THE VITREOUS BASE

TYPE OF TRACTION	CLINICAL SIGNS
Anteroposterior	Vitreous base and retinal trough with or without posterior iris retraction
Anterior circumferential	Radial retinal folds
Anterior perpendicular	Taut and opacified anterior vitreous and funnel-shaped anterior retinal detachment

extend posteriorly from the posterior insertion of the vitreous base.

Anterior perpendicular traction is caused by proliferative vitreous membrane (especially on the posterior vitreous hyaloid) causing transvitreal contraction, which pulls the anterior retina toward the center of the vitreous cavity (Fig. 3). It is recognized by an opacified and taut vitreous surface causing an anterior funnel-shaped retinal detachment. Anterior circumferential and perpendicular traction may occur either with or without anterior displacement of the posterior border of the vitreous base.

Surgical approach—Our surgical approach to anterior proliferative vitreoretinopathy evolved as our knowledge of this condition increased. Early in the series, the posterior periretinal membranes were dissected and the anterior traction was treated indirectly. A high and broad circumferential scleral buckle was used, with demarcation of the anterior membranes by laser endophotocoagulation placed behind the posterior hyaloidoretinal junction.

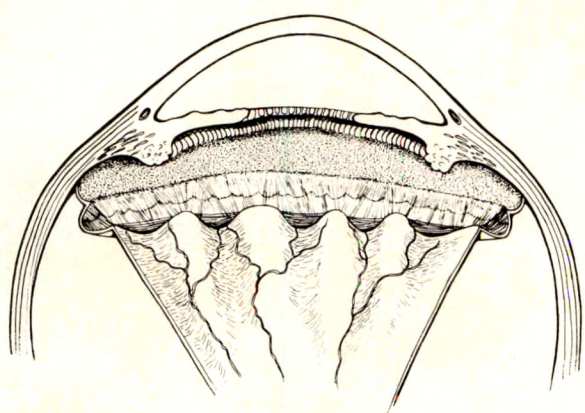


Fig. 2 (Lewis and Aaberg). Anterior proliferative vitreoretinopathy. Circumferential traction caused by a membrane-vitreous complex at the hyaloidoretinal junction and recognized by the radial folds. Anteroposterior traction is also present.

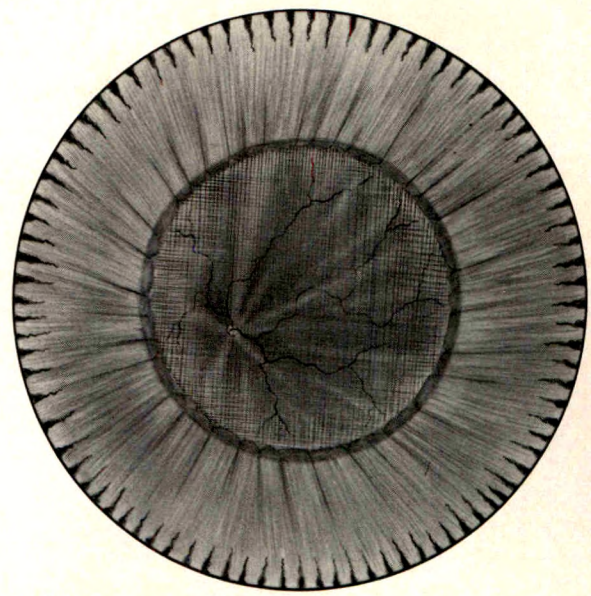


Fig. 3 (Lewis and Aaberg). Anterior proliferative vitreoretinopathy. Perpendicular traction pulling the anterior retina toward the visual axis.

This method did not alter the anterior vitreous base abnormalities. The continued anterior traction sometimes led to retinal redetachment and hypotony after resorption of the gas bubble or evacuation of the silicone oil used for retinal tamponade. We therefore altered our surgical technique to approach directly the anterior proliferative membranes that create the anterior traction.

The locations of the surgical sclerotomies were based on the type and extent of anterior proliferative vitreoretinopathy. In eyes with anterior displacement of the vitreous base, the sclera was perforated with a myringotomy blade, approximately 0.5 to 1.5 mm posterior to the corneoscleral limbus. To prevent entering the retroretinal space, thus creating a retinal dialysis, we avoided a more posterior sclerotomy. In eyes without anterior displacement of the vitreous base but with circumferential or perpendicular anterior traction, the sclerotomies were placed 3 mm posterior to the corneoscleral limbus.

In eyes in which lens removal was necessary to cut anterior membranes, the entire lens cap-

sule was removed, since proliferative tissue was often located on the zonules or lens capsule.[5] Perpendicular traction was relieved by removing the anterior and central vitreous gel.

In eyes with anteroposterior traction the retinal trough at the vitreous base was opened by severing the retina-pars plicata or retina-iris adhesions with scissors. With scleral depression, the anteroposterior vitreous fibers at the vitreous base were cut and trimmed flush with the retina and pars plana.

To relieve the circumferential traction, radial incisions at the posterior border of the vitreous base were made with the right-angle scissors.

The posterior retina was then mobilized by membrane dissection. In contrast to anterior membranes, the posterior proliferative tissue had looser attachments to the retinal surface and was usually completely excised. A fluid-air exchange was then performed to determine whether residual traction was present. Circumferential traction at the vitreous base was the most common form of residual traction. The tractional membranes were released by radial incisions until the air tamponade completely flattened the retina.

Results

Of the 90 patients operated on with vitreoretinal surgery for a rhegmatogenous retinal detachment complicated by proliferative vitreoretinopathy, 56 were men and 34 were women. Of the 92 eyes operated on during the four-year period, 53 (58%) had both anterior and posterior proliferative vitreoretinopathy, while 39 (42%) had only posterior proliferative vitreoretinopathy.

We performed follow-up examinations in 74 patients six months or longer after surgery. The 18 patients we could not examine six months after surgery lived too far away (16 patients) or were deceased (two patients). Forty-two eyes with both anterior and posterior proliferative vitreoretinopathy were examined at least six months postoperatively (mean, 13 months). Thirty-two eyes with only posterior proliferative vitreoretinopathy were examined at least six months postoperatively (mean, 15 months). Only the eyes examined at least six months after surgery were analyzed.

When compared to eyes with just posterior proliferative vitreoretinopathy, eyes with anterior proliferative vitreoretinopathy had a higher percentage of previous intraocular surgery, anterior uveitis, and reduced intraocular pressure (Table 2). All eyes with anterior proliferative vitreoretinopathy had more than one type of anterior traction. Twenty-six eyes (62%) showed all three forms of traction: anteroposterior, circumferential, and perpendicular. In the remaining 16 eyes (38%), the proliferative membranes exerted both anteroposterior and circumferential traction.

The posterior border of the compressed vitreous base was adherent to the anterior vitreous base insertion in 13 eyes (31%), to the pars plicata in 15 eyes (36%), to the posterior iris surface in 13 eyes (31%), and to the pupillary margin in one eye (2%). For purposes of analysis, when the posterior insertion of the vitreous base was anteriorly displaced in more than one sector, we recorded the extent of displacement and its most anterior position. The anteroposterior traction involved four to six clock hours in ten eyes (24%), seven to nine clock hours in 17 eyes (40%), and ten to 12 clock hours in 15 eyes (36%). There was no correlation between the extent of displacement of the posterior insertion of the vitreous base and the number of clock hours affected.

The circumferential traction involved four to six clock hours in 11 eyes (26%), seven to nine clock hours in 16 eyes (38%), and ten to 12 clock hours in 15 eyes (36%).

In 26 eyes (62%), the anterior membranes were associated with retinal breaks. The breaks associated with perpendicular traction were generally larger and easier to visualize than those occurring with anteroposterior or circumferential traction, which were smaller and often not visualized before surgery.

Of 42 eyes with anterior proliferative vitreoretinopathy, 12 (29%) were treated by vitrectomy and a high, broad scleral buckle, with demarcation of the anterior membranes with three rows of laser endophotocoagulation. Twenty-one eyes (50%) were treated by resecting the anterior vitreous with the vitrectomy cutter and directly releasing the anterior traction with scissors dissection. In the remaining nine eyes (21%), a relaxing retinotomy was performed because the anterior traction could not be relieved.

Intraoperative retinal gas tamponade was accomplished in 31 eyes (74%). Silicone oil retinal tamponade was used in 11 eyes (26%). When present, the lens (clear in three eyes and cataractous in nine eyes) was removed to relieve the anterior traction. The membranes

TABLE 2
GROUP CHARACTERISTICS

CHARACTERISTIC	PROLIFERATIVE VITREORETINOPATHY			
	ANTERIOR (N = 42)		POSTERIOR (N = 32)	
	NO.	(%)	NO.	(%)
Eye				
Right	21	(50)	13	(41)
Left	21	(50)	19	(59)
Sex				
Male	26	(62)	23	(72)
Female	16	(38)	9	(28)
Age (yrs)				
Range	13–85		6–82	
Mean	53		49	
Previous intraocular surgery				
Any type	40	(95)	12	(37)
Cataract	30	(71)	6	(19)
With intraocular lens	9	(30)	2	(33)
Without intraocular lens	21	(70)	4	(66)
Vitrectomy				
Anterior (limbal approach)	4	(10)	1	(3)
Posterior (pars plana)	27	(64)	5	(16)
No. of previous pars plana vitrectomies				
1	16	(38)	5	(16)
2	7	(17)	0	(0)
3	4	(10)	0	(0)
Average/eye	1.4		1	
Previous scleral buckle	38	(90)	29	(91)
Time since initial retinal detachment (mos)				
Range	1–150		1–73	
Mean	18		16	
Preoperative visual acuity				
5/200 or better	3	(7)	3	(9)
<5/200	39	(93)	29	(91)
Preoperative anterior chamber inflammation	22	(52)	5	(16)
Preoperative intraocular pressure (mm Hg)				
Range	0–32		9–28	
Mean	11		18	
Posterior grade of proliferative vitreoretinopathy				
C3	17	(40)	9	(28)
D1	4	(10)	12	(37)
D2	6	(14)	3	(9)
D3	15	(36)	8	(25)

causing perpendicular traction were easily excised. The proliferative membranes causing the anterior circumferential and anteroposterior traction were frequently incompletely resected. Nevertheless, the traction was relieved in most eyes in which the anterior membranes were approached directly.

While relieving anterior traction we created retinal breaks in nine eyes. The breaks were marked with diathermy and treated with endophotocoagulation. Since they were supported by the scleral buckle and all traction was relieved, they did not cause postoperative retinal redetachment. Intraoperative vitreous hemorrhage occurred in two eyes (5%). Retroretinal air during fluid-air exchange, because of persisting anterior-posterior traction requiring a relaxing retinotomy, occurred in five eyes (12%).

Except for one eye treated without direct approach to the anterior traction, all of the eyes were intraoperatively reattached.

In eyes operated on with anterior proliferative vitreoretinopathy, the following procedures were performed in the postoperative period: fluid-gas exchange followed by additional laser photocoagulation in ten eyes; repeat vitrectomy with additional anterior membrane dissection, endophotocoagulation, and gas insufflation in three eyes; repeat vitrectomy with additional anterior and posterior membrane dissection, endophotocoagulation, and gas insufflation in three eyes; repeat vitrectomy with additional anterior and posterior membrane dissection, endophotocoagulation, and silicone oil injection in one eye; repeat vitrectomy with additional anterior and posterior membrane dissection, relaxing retinotomy, retinal fixation with tacks, endophotocoagulation, and gas insufflation in one eye; Nd:YAG discission of a pupillary fibrin membrane in one eye; and evacuation of the silicone oil in three eyes.

Eyes that had anterior proliferative vitreoretinopathy had worse anatomic and visual results than eyes with just posterior proliferative vitreoretinopathy (Tables 3 and 4). Of 32 eyes with posterior proliferative vitreoretinopathy, 23 (72%) were totally attached at the last visit in contrast to 25 of 42 eyes (59%) with anterior proliferative vitreoretinopathy. A final visual acuity of 5/200 or better was achieved in 18 of 32 eyes (56%) with only posterior proliferative vitreoretinopathy, but in only 18 of 42 eyes (43%) of eyes with anterior proliferative vitreoretinopathy.

The final rate of total retinal reattachment was higher in eyes in which the anterior proliferative vitreoretinopathy was approached di-

TABLE 3
ANATOMIC RESULTS OF VITREORETINAL SURGERY FOR PROLIFERATIVE VITREORETINOPATHY

	PROLIFERATIVE VITREORETINOPATHY			
	ANTERIOR (N = 42)		POSTERIOR (N = 32)	
ANATOMIC RESULT	NO.	(%)	NO.	(%)
Total retinal reattachment	25	(59)	23	(72)
Retina attached posterior to the scleral buckle	7	(17)	4	(12)
Retina detached posterior to the scleral buckle	10	(24)	5	(16)

TABLE 4
VISUAL RESULTS OF VITREORETINAL SURGERY FOR PROLIFERATIVE VITREORETINOPATHY

	PROLIFERATIVE VITREORETINOPATHY			
	ANTERIOR (N = 42)		POSTERIOR (N = 32)	
FINAL VISUAL ACUITY	NO.	(%)	NO.	(%)
>20/100	5	(12)	5	(16)
<20/100 to >5/200	13	(31)	13	(41)
<5/200	24	(57)	14	(44)
No light perception	0	(0)	0	(0)
Improved	26	(62)	21	(66)
Worse	7	(17)	6	(19)
Unchanged	9	(21)	5	(16)

rectly (16 of 21 eyes, 76%) compared to eyes in which it was bypassed by performing a relaxing retinotomy (five of nine eyes, 56%) or counteracted by placing a high scleral buckle and laser demarcation (four of 12 eyes, 33%) (Table 5). A final visual acuity of 5/200 or better was also achieved in a higher number of eyes in which the anterior membranes were surgically cut (11 of 21 eyes, 52%), when compared to eyes managed with a relaxing retinotomy (four of nine eyes, 44%) or with a high scleral buckle and laser demarcation (three of 12 eyes, 25%) (Table 6).

Discussion

Proliferative vitreoretinopathy is the most common cause of failure of retinal detachment surgery, occurring in approximately 7% of all retinal detachments.[2,6] Modern vitreoretinal surgical techniques are not successful in reattaching 34% to 67% of eyes operated on for proliferative vitreoretinopathy.[7-14] The main reason surgery fails is cellular proliferation in the area of the vitreous base, with subsequent traction on the anterior retina, ciliary body, or

TABLE 5
ANATOMIC RESULTS IN EYES WITH ANTERIOR PROLIFERATIVE VITREORETINOPATHY ACCORDING TO THE SURGICAL TREATMENT RECEIVED

	TOTAL REATTACHMENT		REATTACHMENT POSTERIOR TO THE BUCKLE		DETACHMENT POSTERIOR TO THE BUCKLE	
SURGICAL PROCEDURE	NO.	(%)	NO.	(%)	NO.	(%)
Vitrectomy, high buckle, laser demarcation of anterior membranes (N = 12)	4	(33)	4	(33)	4	(33)
Vitrectomy, scleral buckle, direct surgical approach to anterior membranes (N = 21)	16	(76)	2	(10)	3	(14)
Vitrectomy, scleral buckle, relaxing retinotomy (N = 9)	5	(56)	1	(11)	3	(33)

TABLE 6
VISUAL RESULTS IN EYES WITH ANTERIOR PROLIFERATIVE VITREORETINOPATHY ACCORDING TO THE SURGICAL TREATMENT RECEIVED

SURGICAL PROCEDURE	VISUAL ACUITY >20/100 NO.	(%)	<20/100 TO >5/200 NO.	(%)	<5/200 NO.	(%)
Vitrectomy, high buckle, laser demarcation of anterior membranes (N = 12)	1	(8)	2	(17)	9	(75)
Vitrectomy, scleral buckle, direct surgical approach to anterior membranes (N = 21)	4	(19)	7	(33)	10	(48)
Vitrectomy, scleral buckle, relaxing retinotomy (N = 9)	0	(0)	4	(44)	5	(56)

both. Without relief of anterior traction, these eyes progress to a total retinal detachment and often to hypotony and atrophia bulbi.

In an attempt to improve the prognosis of these patients over the last four years we paid particular attention to membrane traction in the region of the vitreous base. We found that of eyes operated on with a combination of vitreous and retinal surgery for a rhegmatogenous retinal detachment complicated by proliferative vitreoretinopathy from 1983 to 1986, 58% demonstrated both anterior and posterior proliferation. Previous cataract or vitreous surgery for retinal detachment, lower intraocular pressure, and anterior chamber inflammation were more common in eyes with an anterior proliferative vitreoretinopathy. In eyes with an intact vitreous gel, the cells proliferate and contract on both sides of the sensory retina, on the posterior vitreous surface, and in the central vitreous gel. Conversely, in eyes in which the vitreous has been altered by intravitreal gas injection, cataract extraction with a ruptured anterior hyaloid, or by a partial or total vitrectomy, cells disperse into the compressed or unexcised anterior vitreous where they proliferate and cause detachment of the anterior retina and ciliary body. Because of the strong adhesion between the vitreous and the retina at the vitreous base, cells proliferate within the vitreous humor as well as at the hyaloidoretinal junction.

Because of the frequency of anterior proliferation and traction, we aggressively removed as much anterior vitreous as technically possible, even in eyes with only posterior proliferative vitreoretinopathy. In aphakic eyes, we excised all possible anterior vitreous to the retinal surface. In phakic eyes, an extensive removal of the anterior vitreous is not possible. Only by removing the lens can vitrectomy in the area of the vitreous base be performed so as to eliminate structures that cells will proliferate on.

Indirect treatment of anterior proliferative vitreoretinopathy by a high encircling scleral buckle and demarcation of anterior membranes with laser endophotocoagulation was the least successful method of treatment. A total anatomic reattachment was achieved in four of 12 eyes (33%) and a final visual acuity of 5/200 or better in only three of 12 eyes (25%). In all of these eyes, the posterior retinal traction was relieved by dissection of posterior periretinal membranes. This method can be successful in some eyes with anterior circumferential or perpendicular traction. However, we found that in eyes with anterior displacement of the vitreous base by anteroposterior traction, the anterior retina would reattach on the scleral buckle but the posterior retina was foreshortened by the anterior retinal trough and was not completely flat.

The release of the anterior traction by a direct surgical approach carried the best chances for anatomic reattachment and restoration of ambulatory vision. Unfortunately, despite anterior membrane dissection, the anterior traction cannot be relieved in all eyes and a relaxing retinotomy may be required to flatten the retina in some cases. The anatomic and visual results in these eyes are reduced.

Understanding the full extent of proliferative vitreoretinopathy and using a direct surgical approach to the anterior proliferative tissue has improved the success rate of these difficult cases.

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OPHTHALMIC MINIATURE

In the outer room the two women knitted black wool feverishly. People were arriving, and the younger one was walking back and forth introducing them....Often far away there I thought of these two, guarding the door of Darkness, knitting black wool as for a warm pall, one introducing, introducing continuously to the unknown, the other scrutinizing the cheery and foolish faces with unconcerned old eyes. *Ave*! Old knitter of black wool. *Morituri te salutant*. Not many of those she looked at ever saw her again.

Joseph Conrad, *Heart of Darkness*
New York, Doubleday & Company, 1910, p. 74

The Pathogenesis of Tears of the Retinal Pigment Epithelium

Elaine L. Chuang, M.D., and Alan C. Bird, M.D.

We compared drusen in the fellow eye of patients with unilateral retinal pigment epithelial tears with those in an age- and sex-matched group of patients with unilateral primary neovascular disciform lesions. In the fellow eye of patients with tears, drusen were more confluent and manifested less fluorescence on angiography than in the comparison group. These observations are in accord with the concept that Bruch's membrane represents a significant barrier to fluid flow, and that fluid beneath detached pigment epithelium is derived in part or wholely from the pigment epithelium.

RIPS OR TEARS of the retinal pigment epithelium have been recognized increasingly as a cause of severe loss of central vision in age-related macular degeneration.[1-16] Patients experience the sudden onset of distortion or a precipitous drop in central acuity coincident with the tear if the fovea is involved. The typical acute fundus appearance is that of an abrupt discontinuity in the pigment epithelium at its border of previous detachment. The consequent defect in the pigmented monolayer and the production of redundant folds of the remaining detached tissue lead to a characteristic acute angiographic appearance of hyperfluorescence in the bed of the tear, with adjacent hypofluorescence corresponding to the retracted mound of pigment epithelium. With time, progressive scarring and other alterations render the origin of the lesion more difficult to recognize.[15]

Recently, tears have been shown to occur bilaterally more frequently than would be predicted by chance alone.[16] This could imply that the age-related changes in Bruch's membrane in eyes destined to manifest tears are different from those present in eyes not at risk of sustaining this complication. In this study, we compared the changes in the fellow eye of patients with unilateral tears of the pigment epithelium with those changes seen in the fellow eyes of patients with unilateral neovascular disciform lesions. Our primary goal was to contribute to the understanding of the pathogenesis of pigment epithelial detachments that are destined to tear, and perhaps of pigment epithelial detachments in general.

Patients and Methods

We reviewed our clinical and photographic records between 1976 and 1986 to identify patients in whom the diagnosis of a pigment epithelial tear was made in one eye and in whom the contralateral eye had adequately recorded drusen in the posterior pole. Fellow eyes with evidence of exudative lesions or significant pigmentary atrophy were excluded.

Thirty-one patients with unilateral tears of the retinal pigment epithelium met these criteria. For comparison, a patient group with unilateral neovascular disciform degeneration and contralateral drusen was matched by age and sex as well as by the year of first clinical examination (in order to reduce differences resulting from changes in photographic and angiographic techniques). There were 17 women and 14 men in each group. They ranged in age from 55 to 80 years (mean, 71 and 70 years in women and men, respectively) in the tear group, and 56 to 83 years (mean, 69 and 67 years in women and men, respectively) in the disciform group.

Color photographs and fluorescein angiograms of each group were analyzed by both of us independently for size, density, and early

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and late angiographic behavior of macular drusen; one of us was masked from the diagnosis in the eye with visual loss. The posterior pole was divided into two areas: outside and within 1,600 μm of the foveola. The drusen were divided according to size (0 to 50 μm, 50 to 500 μm, and greater than 500 μm), and distribution was classified as scattered, subconfluent, or confluent. Fluorescence of drusen was assessed as equal to choroidal fluorescence, slightly greater than choroidal fluorescence, or brightly fluorescent. In most cases the drusen were uniform in size, distribution, and fluorescence in each area of the macula; when this was not the case the classification was determined by the largest, most densely packed and most fluorescent lesions. A few eyes were not included in each category of analysis because of the lack of transit or late photographs.

Drusen were present in both eyes of five patients who were examined before the development of a pigment epithelial tear in either eye.

The number of eyes in each group was determined according to the above criteria. The Yates' corrected chi square test was applied to the data to assess the probability of these results occurring by chance alone.

Results

Drusen displayed a greater degree of confluence in fellow eyes of patients with pigment epithelial tears compared to fellow eyes of patients with primary neovascular lesions (Table 1). This was true in the central macula ($P = .032$), but the difference between the two patient groups did not reach a statistically significant level in the peripheral macula ($P = .240$). There was a tendency for drusen to be larger in the eye contralateral to eyes with tears in the central macula, but the difference was not statistically significant.

The angiographic behavior of drusen in the setting of tears was found to differ significantly from that in fellow eyes of neovascular disciform lesions (Table 2). In transit photographs of both the central and peripheral macula, the degree of fluorescence of drusen in fellow eyes of those with rips was less than that in fellow eyes of those with primary neovascular disciform lesions ($P < .001$ and $P < .006$, respectively) (Figure). Similarly, late staining of macular drusen was less intense in the study patients than in the comparison group centrally and peripherally ($P < .0001$ and $P < .0002$, respectively) (Figure).

The findings in the five eyes in which examination of drusen was performed before the development of a pigment epithelial detachment, which then tore, were not different from those of the 31 contralateral study eyes.

Discussion

These results indicate that age-related changes at the level of Bruch's membrane in eyes destined to suffer rips are different from those at risk of developing primary neovascular lesions. The properties of the drusen probably reflect the nature of the changes in Bruch's membrane that place the eye at high risk of suffering a retinal pigment epithelial detachment, which will eventually tear.

It would have been desirable to characterize the nature of these alterations in eyes before development of the pigment epithelial detachment. However, because of the nature of this study, only a limited number of such eyes were observed. It was for this reason that we examined drusen in the fellow eye of patients with tears. The relevance of an analysis of drusen is based on the following rationale. Drusen are the manifestation of age-related change in the region of Bruch's membrane that is most amenable to analysis. It has been shown previously that fellow eyes in patients with unilateral pigment epithelial tears are at high risk of sustaining a similar lesion.[16] Furthermore, since there is remarkable symmetry of drusen in the elderly,[17,18] it is reasonable to assume that drusen in the fellow eye to one with a unilateral tear would be similar to those that existed in the first eye before detachment of the pigment epithelium.

The significance of the hypofluorescence of drusen may be assessed in relationship to concepts of pathogenesis of retinal pigment epithelial detachments. Originally, it was considered likely that detachment was induced by the passage of fluid from the choroid through Bruch's membrane, the physical attachment of the pigment epithelium having been disturbed by the accumulation of debris on the inner surface of Bruch's membrane.[19] This presupposes that hydrostatic pressure in the choroid is higher than that in the retina, and yet the

TABLE 1
COMPARISON OF SIZE AND DENSITY OF MACULAR DRUSEN IN FELLOW EYES*

GROUP	LOCATION OF DRUSEN	SIZE 0-50 μM	SIZE 50-500 μM	SIZE >500 μM	DENSITY SCATTERED	DENSITY SUBCONFLUENT	DENSITY CONFLUENT
Study group†	Central macula	0	25	6	6	18	7
	Peripheral macula	2	27	1	19	10	1
Comparison group‡	Central macula	3	26	2	15	11	5
	Peripheral macula	3	25	1	23	6	0

*Numbers of eyes in central (0 to 1,600 μm from foveola) and peripheral (>1,600 μm from foveola) macula segregated by size and density of drusen. Three fellow eyes lacked peripheral macular drusen: one from the tear group and two from the neovascular disciform lesion group.

†Fellow eyes in patients with unilateral retinal pigment epithelial tears.

‡Fellow eyes in patients with unilateral neovascular disciform lesions.

evidence suggests that the reverse is the case.[20]

Recently, it has been suggested that fluid in the subpigment epithelial space may be derived, at least in part, from the pigment epithelium rather than the choroid.[21] It is widely accepted that fluid crosses the retinal pigment epithelium from the neurosensory retina toward Bruch's membrane because of active transport of ions. It was argued that age-related changes in Bruch's membrane might cause increased resistance to water flow, causing fluid to accumulate in the subpigment epithelial space. It was further postulated that this reduced permeability of Bruch's membrane to water might result from deposition of lipid and lipoprotein, and that the resistance could be higher in some eyes than in others. The concept of the pigment epithelial pump causing detachment of the pigment epithelium from a hydrophobic Bruch's membrane is analogous to dome formation of a pigment epithelial monolayer when cultured on plastic.[22]

Previous studies of human ocular material lend some credibility to these postulates. There

TABLE 2
COMPARISON OF FLUORESCEIN ANGIOGRAPHIC STAINING OF MACULAR DRUSEN IN FELLOW EYES*

GROUP	PHASE OF ANGIOGRAM	FLUORESCENCE CENTRAL MACULA SAME AS CHOROID	CENTRAL MACULA MINIMALLY BRIGHTER THAN CHOROID	CENTRAL MACULA BRIGHT	PERIPHERAL MACULA SAME AS CHOROID	PERIPHERAL MACULA MINIMALLY BRIGHTER THAN CHOROID	PERIPHERAL MACULA BRIGHT
Study group†	Early	10	3	0	7	6	0
	Late	2	23	4	2	20	7
Comparison group‡	Early	3	6	12	3	7	9
	Late	2	6	23	2	5	22

*Numbers of eyes in central (0 to 1,600 μm from foveola) and peripheral (>1,600 μm from foveola) macula with early and late staining of drusen.

†Fellow eyes in patients with unilateral retinal pigment epithelial tears.

‡Fellow eyes in patients with unilateral neovascular disciform lesions.

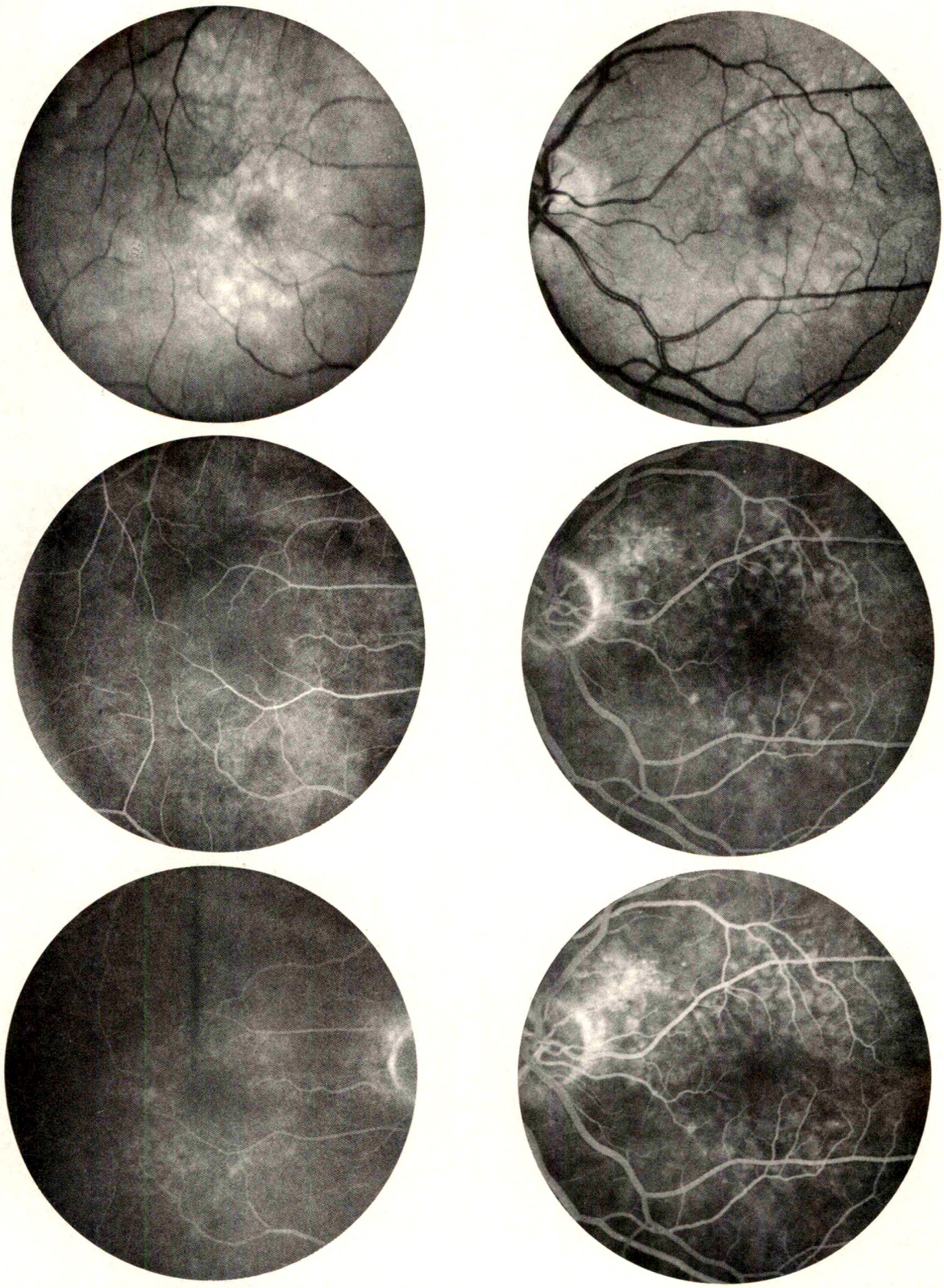


Figure (Chuang and Bird). Red-free photographs and early and late fluorescein angiograms of the fellow eyes of a patient with a pigment epithelial rip (left) and of a patient with unilateral vascular disciform macular disease (right). In the former the drusen remain hypofluorescent, whereas in the latter the drusen are hyperfluorescent throughout the study.

is evidence of variation in the hydrophobicity of drusen,[21] and plaques of lipid have been identified in Bruch's membrane of eyes from the elderly.[23] Ultrastructural studies have been interpreted as showing evidence of impedance to fluid flow in the presence of a "basal linear deposit" on the inner surface of Bruch's membrane.[24] Finally, investigations into changes in the hydraulic conductivity of Bruch's membrane in human eyes show a marked fall in the ability of water to move across Bruch's membrane with age.[25]

Retinal pigment epithelial detachments that are destined to tear tend to become progressively larger and more highly detached, thereby generating sufficient tangential stress in the detached tissues to cause a rupture.[11] This suggests that it is in these lesions that the resistance to water flow across Bruch's membrane would be highest. The hypofluorescence of drusen observed in this study reflects limited entry of fluorescein into the lesions because of their hydrophobicity.[21] The proposed hydrophobicity and confluent tendency of such drusen imply that there would be high resistance to water flow at the level of Bruch's membrane in these eyes.

Much of the evidence concerning the origin of tears and detachments of the retinal pigment epithelium is circumstantial, and many pathogenetic factors are undoubtedly involved. However, the concept of increased resistance to fluid outflow from the subpigment epithelial space is attractive in that it accounts for three observed clinical phenomena that remain unexplained to date. First, it has been shown that in lesions destined to tear, the appearance of fluorescence is slowed during angiography.[1,5,6] Because it is water soluble, fluorescein would pass slowly through a lipid-laden Bruch's membrane from the choroid into the subpigment epithelial space. Secondly, flattening of pigment epithelial detachment occurs in a large percentage of lesions after photocoagulation[26]; by destroying a proportion of retinal pigment epithelial cells, treatment would effectively reduce the quantity of fluid being actively pumped into the subpigment epithelial space. Finally, spontaneous flattening of pigment epithelial detachments in the elderly is accompanied by loss of vision.[9] Both would result from metabolic failure of the pigment epithelium as was proposed by Casswell, Kohen, and Bird.[9]

It has been suggested that subpigment epithelial neovascularization is essential to the pathogenesis of pigment epithelial tears.[6] Although new vessels are undoubtedly common in these lesions, the evidence at present suggests that subpigment epithelial neovascularization is not universal in pigment epithelial detachments.[15] Growth of blood vessels from the choroid toward the retina would occur in response to separation of pigment epithelium from Bruch's membrane, if, as has been reported by Glaser and associates,[27] the pigment epithelium is responsible for suppressing vascularity of neighboring structures. Subpigment epithelial neovascularization may thus occur as a secondary phenomenon. Interestingly, this sequence of events was originally proposed by Gass in his 1967 monograph.[19] This is not to deny the potential importance of choroidal neovascularization as a determinant of the clinical behavior of pigment epithelial detachments and tears, but does argue against this process as the primary pathogenetic mechanism in these lesions.

Two further considerations may be relevant. Blood vessels growing on the inner surface of Bruch's membrane would not cause large detachments unless there was significant resistance to water flow out of the cavity at the level of Bruch's membrane. Plasma constituents leaking from these blood vessels into the subpigment epithelial space may compromise further the permeability of Bruch's membrane. Finally, these concepts do not exclude loss of adhesion of pigment epithelium to Bruch's membrane as a possible contributory mechanism in the pathogenesis of pigment epithelial detachments.

Future histopathologic, biochemical, and prospective clinical studies will elicit more information on the nature of the age-related changes at the level of Bruch's membrane. If more evidence for hydrophobicity of Bruch's membrane is found, and further support is derived for the retinal pigment epithelium as a source, or at least, a major contributor to fluid in the subpigment epithelial space, there may be therapeutic implications. Treatment directed at reducing the pigment epithelial pump or increasing the permeability of Bruch's membrane might reduce the risk not only of tears complicating retinal pigment epithelial detachments, but also of pigment epithelial detachments in general.

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Pigmentary Changes in Acquired Retinoschisis

Mark DiSclafani, M.D., Alan Wagner, M.D., William Humphrey, M.D., and James Valone, Jr., M.D.

We reviewed retrospectively the records of patients referred for retinal examination and found 375 eyes (233 patients) with acquired retinoschisis. Of the 375 eyes, 85 had outer layer retinal breaks, 27 had retinal detachments, and 29 had pigmentary lines. Twenty-five of the 29 pigmentary lines (86.2%) demarcated either retinal detachment or outer retinal layer breaks.

ACQUIRED RETINOSCHISIS is a peripheral retinal degeneration characterized by splitting of the retina at the outer plexiform layer. This condition is found in 7% of the population aged 40 years or older.[1] It is usually bilateral, and the temporal retina is most commonly involved.[1-3]

Complications secondary to retinoschisis include breaks of both inner and outer retinal layers, clinical and subclinical retinal detachment, and, rarely, posterior extension to the macula. Pigmentary changes, sometimes referred to as demarcation lines, have been associated with uncomplicated retinoschisis[1,4-6] and with complications such as outer layer breaks or retinal detachment.[3,7-10]

Pischel[11] and others[3,9,12] suggested that pigmented demarcation lines in the setting of retinoschisis may indicate retinal detachment. Pigmented demarcation lines have also been reported in uncomplicated retinoschisis.[4,10,13] Therefore, controversy exists as to the significance of pigmentary changes associated with acquired retinoschisis. This study was undertaken to examine the incidence of pigmentary change and its relationship to complications of retinoschisis, such as retinal breaks and retinal detachment.

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Patients and Methods

We reviewed retrospectively the records of patients who had been referred for retinal examination between 1976 and 1986 for the presence of acquired retinoschisis. The patients had been examined by indirect ophthalmoscopy, scleral depression, and, when applicable, Goldmann three-mirrored contact lens. Fundus drawings and clinical records were reviewed for laterality, extent of retinoschisis in clock hours and posteriorly, complications such as retinal breaks and detachment, and the presence of pigmentary changes.

Results

Two hundred thirty-three patients (375 eyes) had acquired retinoschisis. The average patient age was 61.5 years. The condition was bilateral in 142 patients (60.9%). The circumferential extent of retinoschisis averaged 2.5 clock hours per retinoschisis cavity. Posterior extension of retinoschisis to the macula occurred in only one case (0.04%). The inferotemporal quadrant was involved in 314 eyes (83.7%), the superotemporal quadrant in 40 eyes (10.7%), the inferonasal quadrant in 13 eyes (3.5%), and the superonasal quadrant in eight eyes (2.1%).

Retinal breaks were present in 104 eyes (27.7%) with acquired retinoschisis. Ninety-six eyes (25.6%) had either inner or outer layer breaks. Outer layer breaks alone occurred in 85 eyes (22.7%). Inner layer breaks alone were noted in 11 eyes (2.9%). Breaks of outer and inner layers were detected in eight eyes (2.1%).

Retinal detachments, most of them subclinical, occurred in 27 eyes (7.2%). One detachment involved the macula. Seventeen retinal detachments (62.9%) were associated with outer layer breaks only. Eight detachments (29.6%) had double layer breaks. In two detachments (7.5%), no breaks could be detected.

Pigmentary changes or demarcation lines oc-

curred in 29 of 375 eyes with retinoschisis (7.7%). Thirteen eyes with demarcation lines (44.8%) had associated retinal detachment, and 12 eyes with pigmentary changes (41.4%) had associated outer layer breaks alone. In four eyes (13.8%) pigmentary changes were not associated with either breaks or retinal detachment.

Discussion

Acquired retinoschisis is thought to be preceded by peripheral cystoid degeneration in which microcysts enlarge and become confluent to separate the retina at the outer plexiform layer into two layers.[5,14] The characteristics of retinoschisis, both clinical and histologic, have been well described. Most observers agree that the condition is usually seen in older individuals, is more often bilateral, and is usually temporal in location.[1-3] Breaks can occur in either layer. Both clinical and subclinical retinal detachment can occur. Our study supports all of these observations. Characteristics less well agreed upon include the incidence and significance of pigmentary change associated with retinoschisis.

A histologic study by Yanoff and Fine[15] of pigmentary demarcation lines seen in retinal detachment showed proliferative pigment epithelial cells and laying down of basement membrane.[16] Straatsma and Foos[8] in their histologic study of retinoschisis detected outer layer holes with surrounding retinal detachment and pigment disturbances similar to that described by Yanoff and Fine in association with retinal detachment. In another study of retinoschisis, Foos[7] described outer layer holes with surrounding detachment and delimiting pigmentary disturbance. Foos also described an area of chorioretinitis at the edge of the detachment, which may contribute to the formation of a clinical demarcation line.

Linear pigmentary changes, often termed demarcation lines, are known to occur at the posterior border of retinal detachments after three months.[13,15,16] They may also be seen in resolved retinal detachment when the normally transparent neurosensory retina is reopposed to pigment epithelium.[16] However, the incidence and significance of pigmentary change in retinoschisis is controversial. Pischel,[11] Duke-Elder and Dobree,[5] and Okun and Cibis[4] noted the presence of pigmented demarcation lines in uncomplicated retinoschisis, while others have observed demarcation lines rarely, if ever, in uncomplicated retinoschisis.[4,7,12,13,17] Dobbie[9] reported true demarcation lines in only those cases of retinoschisis with retinal detachment. Byer[17] reported four cases of demarcation lines with three combined retinoschisis-retinal detachments. Both emphasized that pigmentary demarcation lines suggested a complicated form of retinoschisis. Of the 29 eyes with pig-

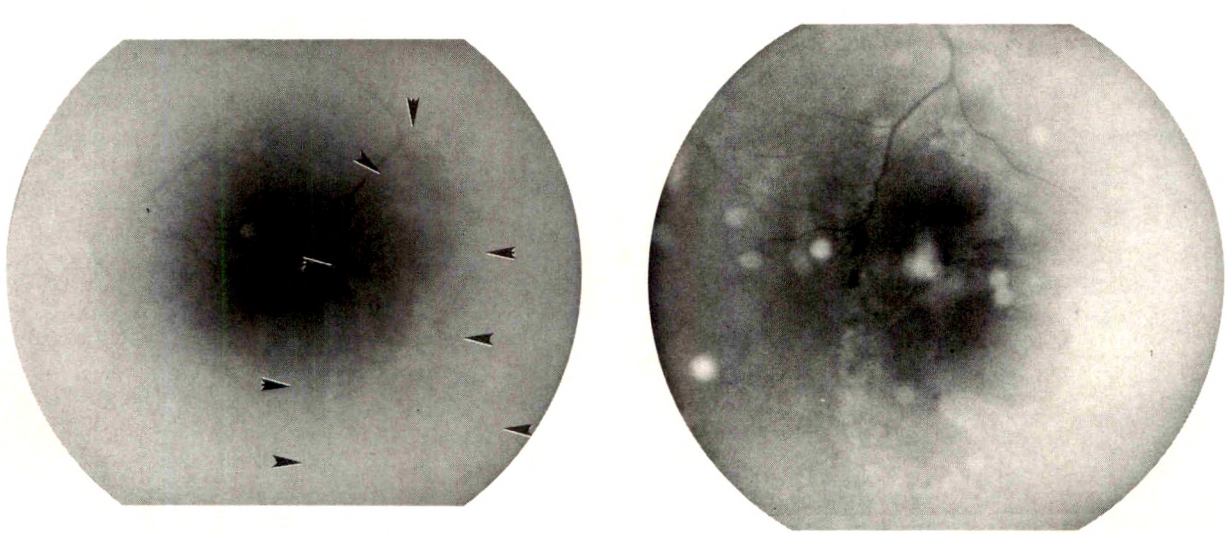


Figure (DiSclafani and associates). Left, Area of acquired retinoschisis with outer layer break and subclinical retinal detachment (outlined by arrowheads) before formation of demarcation line. Right, Five years later, after formation of clinical demarcation line.

mented demarcation lines in our series, 44.8% delimited retinal detachment while another 41.4% were seen surrounding outer layer holes without definite clinical detachment. Therefore, 86.2% of pigmentary changes were associated with either retinal detachment or outer layer breaks (Figure). Pigmentary changes, when associated with acquired retinoschisis, should alert the examiner to the possible existence of these complications and prompt more frequent follow-up.

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Leukemic Involvement of the Optic Nerve

Hirotoshi Nikaido, M.D., Hiromu Mishima, M.D., Hideyuki Ono, M.D., Kanji Choshi, M.D., and Hiroo Dohy, M.D.

We studied five cases of leukemia with invasion of the optic disk and optic nerve. Two patients had acute lymphoblastic leukemia and three had acute myelogenous leukemia. All patients received intrathecal injections of chemotherapeutic drugs including methotrexate, cytarabine, and prednisolone. Three patients underwent irradiation therapy of the whole brain and optic nerve. While initial improvement in the ophthalmic abnormalities, such as optic disk edema, flame-shaped retinal hemorrhages, and dilation of the retinal vein, was noted, optic atrophy was later found in all eyes.

MOST OF THE ocular involvement in leukemia can be related to direct invasion by leukemic cells. Direct invasion of the orbit is common, but involvement of the optic nerve, uveal tract, and retina is rare. However, other hematologic abnormalities associated with leukemia have ophthalmic complications; for example, anemia (leukemic retinopathy) and hyperviscosity (microaneurysm formation, capillary closure, and retinal neovascularization) can produce ocular complaints.

Cases of acute leukemia with involvement of the central nervous system are becoming more frequent because of the increased survival rates associated with more effective chemotherapy, especially in acute myelogenous leukemia. Therefore, the number of patients with invasion of the optic nerve as the significant finding of central nervous system leukemia is increasing.

We studied five cases of leukemia with invasion of the optic disk and optic nerve. Two patients had acute lymphoblastic leukemia and three had acute myelogenous leukemia. All patients received intrathecal injections of methotrexate, cytarabine, and prednisolone. Three patients underwent irradiation of the whole brain including the optic nerve. Herein we discuss the efficacy of chemotherapeutic drugs injected into the intrathecal space to attack the malignant cells in the optic nerve.

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Case Reports

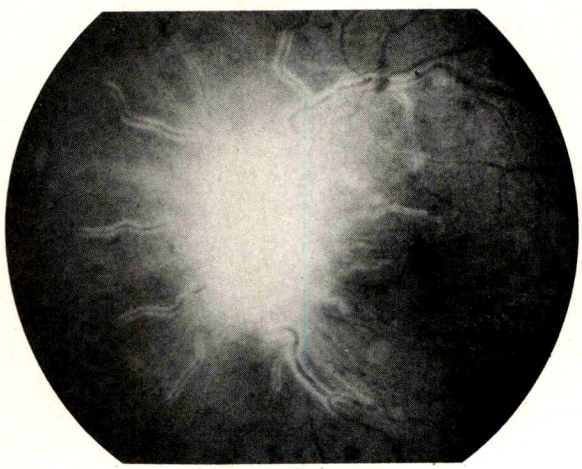
Case 1

Acute lymphoblastic leukemia was diagnosed in this 29-year-old woman in October 1979. She was treated with cytotoxic drugs including vincristine, cytarabine, 6-mercaptopurine, and prednisolone. Systemic remission was achieved in March 1980.

She complained of left facial nerve palsy in June 1980. A lumbar puncture was performed because of the suspicion of central nervous system involvement with acute lymphoblastic leukemia. The tap demonstrated 1,000 lymphoblasts/ml in her spinal fluid. An intrathecal injection of cytotoxic drugs was administered with systemic chemotherapy.

After complete remission of the central nervous system symptoms, she complained of impaired vision in her left eye. Her best corrected visual acuity was R.E.: 30/20 and L.E.: 20/16. Ophthalmoscopy showed a normal right optic disk and retina. On the left, the optic disk was markedly swollen, yellow-white in color, and the retinal veins were dilated (Fig. 1, top). Fluorescein angiography disclosed an increase of fluorescence over the entire surface of the left optic disk and peripapillary retina (Fig. 1, bottom).

Three weeks later visual acuity in the left eye was hand motions. Computed tomography showed a swollen left optic nerve (Fig. 2). Radiotherapy was performed to the whole brain including the orbit (2,600 rad), and addi-



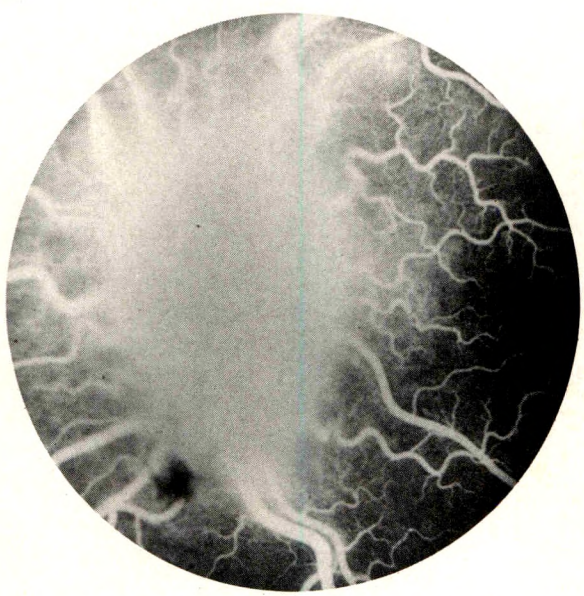


Fig. 1 (Nikaido and associates). Case 1. Top, The left optic disk is swollen and yellow-white, and the retinal veins are markedly dilated. Bottom, Late fluorescein fundus angiogram shows a marked increase of fluorescence over the entire surface of the disk and peripapillary retina.

tional radiation therapy was administered to the left orbit (1,000 rad). After a temporary improvement in visual acuity in her left eye, the left optic disk atrophied.

Case 2

A 27-year-old woman complaining of gingival bleeding was admitted with a suspicion of leukemia on July 23, 1980. Histologic staining of sternal bone marrow showed acute myelogenous leukemia. She received systemic

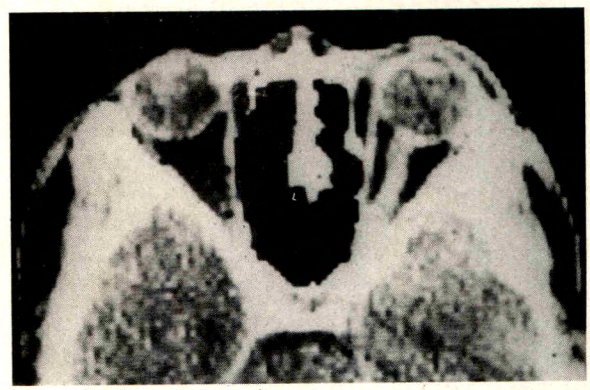


Fig. 2 (Nikaido and associates). Case 1. Computed tomography showing the swollen left optic nerve.

enocitabine, daunorubicin, 6-mercaptopurine, and prednisolone. Apparent remission was achieved. On Oct. 1, 1980, results of a lumbar puncture showed leukemic cells in the cerebrospinal fluid. She was treated with two series of intrathecal cytotoxic drugs. On Nov. 22, she noticed floating spots in her right visual field. Ophthalmoscopic examination showed optic disk edema and elevation, with widespread vitreal hemorrhages in the right eye. Her left fundus was normal. On Dec. 1, 1980, and Jan. 12, 1981, computed tomography showed normal optic nerves bilaterally. On Jan. 30, 1981, she died of respiratory failure.

Case 3

A 43-year-old woman with diabetes who complained of headaches was admitted on Nov. 9, 1981. Acute myelogenous leukemia was diagnosed. On Nov. 12, she noticed a decrease in visual acuity. Ophthalmoscopy showed swelling of the right optic nerve head and widespread retinal hemorrhages. In her left eye, there were retinal hemorrhages with vitreal hemorrhage and a swollen optic disk. Results of lumbar puncture showed a pressure of 350 mm H_2O, with no leukemic cells. She was treated with cytotoxic drugs including enocitabin, daunorubicin, vincristine, 6-mercaptopurine, and prednisolone. She also received two intrathecal injections of cytotoxic drugs. After this therapy, complete systemic remission was noted. However, increased retinal and massive vitreal hemorrhages were seen. In February 1982 her bone marrow aspirate showed a relapse of acute myelogenous leukemia, and systemic chemotherapy was resumed. On June 16, visual acuity was R.E.: light perception and L.E.: no light perception.

There was atrophy of both optic disks, white retinal vessels, and no hemorrhage. On Aug. 13, she died of respiratory failure.

Case 4

Acute myelogenous leukemia was diagnosed in this 22-year-old man in December 1981. He was treated with several courses of systemic chemotherapy combined with several courses of intrathecal cytotoxic drugs. Systemic remission of the acute myelogenous leukemia was noted. On May 30, 1982, he noted severe photopsia in his right eye. On June 10, he noticed a central scotoma of the right eye. Best corrected visual acuity was R.E.: 20/200 and L.E.: 20/16. He had a large scotoma in the upper half of his right visual field, including the central field. Ophthalmoscopy showed that the right optic disk was slightly swollen and had an indistinct margin (Fig. 3, top). His left eye was normal. Fluorescein angiography of the right fundus demonstrated a slight leakage of fluorescence over the entire surface of the optic disk and peripapillary retina (Fig. 3, bottom). On June 11, visual acuity in his right eye was improved to 20/16 after systemic administration of betamethasone. Computed tomography showed a markedly swollen right optic nerve (Fig. 4). His visual acuity worsened and he developed overt central nervous system leukemia. Intrathecal cytotoxic drugs were administered in combination with systemic chemotherapy. A complete remission was noted. However, visual acuity in the right eye was reduced to light perception. On Sept. 9, radiotherapy to the whole brain was begun, including the orbit (1,000 rad), and to the whole spine (2,000 rad). After this therapy, the right optic disk became pale, but there were no signs of leukemia in his eyes. The acute myelogenous leukemia was in remission for three years.

Case 5

Acute lymphoblastic leukemia was diagnosed in this 17-year-old boy in January 1982. He had been treated with systemic chemotherapy combined with 11 courses of intrathecal cytotoxic drugs. In February 1984 the third recurrence of systemic acute lymphoblastic leukemia was diagnosed. On April 18, he noticed floating spots in his right visual field. He came in for an examination one week later. Best corrected visual acuity was R.E.: 20/16 and L.E.: 20/20. Ophthalmoscopy showed a swollen right optic disk with dilated retinal veins (Fig. 5). The nasal margin of his left optic disk was indistinct, and he had a turbid peripapillary retina. We started radiotherapy to the whole brain including both orbits (2,260 rad), along with systemic chemotherapy. After treatment, results of ophthalmoscopy were normal. The patient died of multiple organ failure on June 20.

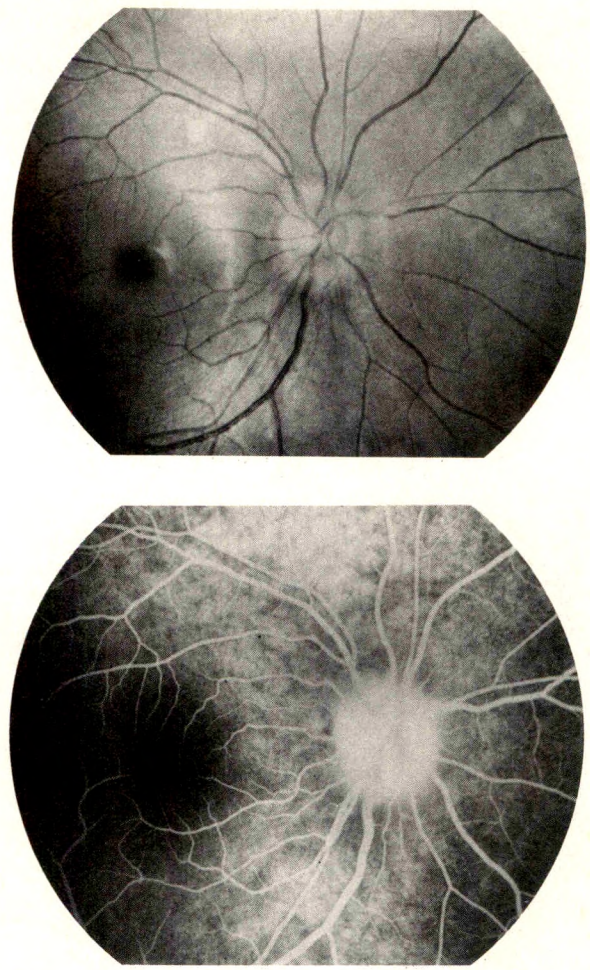


Fig. 3 (Nikaido and associates). Case 4. Top, The right optic disk is slightly swollen, with an indistinct margin. Bottom, Fluorescein fundus angiography shows a slight increase in fluorescence over the entire surface of the optic disk.

Discussion

The number of patients with leukemic involvement of the central nervous system as a complication of acute leukemia is increasing with the longer survival rate associated with more effective chemotherapy.[1-7] Optic nerve

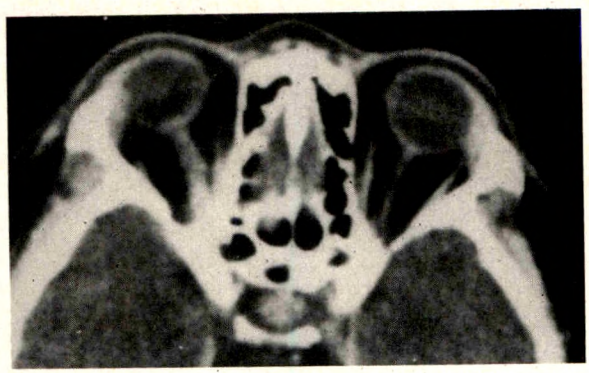


Fig. 4 (Nikaido and associates). Patient 4. Computed tomography showing a swollen right optic nerve.

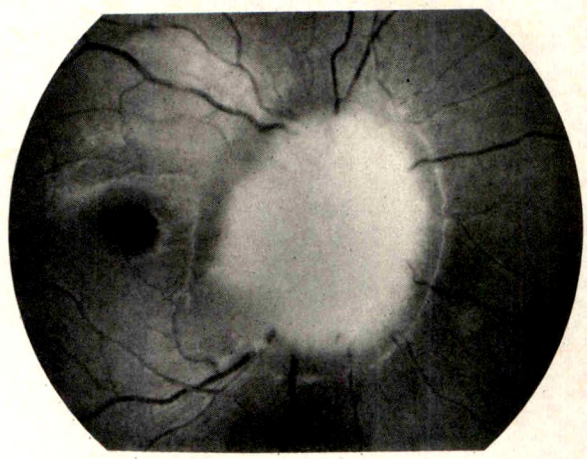


Fig. 5 (Nikaido and associates). Case 5. The right optic disk is swollen, with dilated retinal veins.

invasion is considered to be one of the significant clinical findings of central nervous system leukemia. The frequency of optic nerve involvement is increasing in acute lymphoblastic leukemia as well as in other types of leukemia.

Optic nerve invasion and facial nerve palsy are signs suggesting the existence of central nervous system leukemia. They can be the first sign of central nervous system involvement, or they may be later symptoms. Of our five patients, we detected leukemic cells in the cerebrospinal fluid in three (proof of central nervous system involvement) and recognized facial nerve palsy in two. However, we could not establish any correlation between the order of appearance of optic nerve invasion, facial nerve palsy, and proof of central nervous system involvement (Table).

The optic nerve floats in the cerebrospinal fluid and is nourished by this fluid. The presence of the blood-brain barrier shields the optic nerve from any systemically administered chemotherapeutic drugs. Consequently, direct intrathecal injection of cytotoxic drugs with irradiation therapy is necessary for effective treatment of optic nerve involvement in leukemia. The optic nerve is usually considered relatively insensitive to irradiation therapy, whereas leukemic cells are quite radiosensitive. Several previous studies have shown only partial or no successful results from the intrathecal injection of cytotoxic drugs[2,6]; therefore, the optic nerve is considered a pharmacologic sanctuary from leukemic therapy.[4] Our cases also demonstrated the limitations of intrathecal cytotoxic drugs in the treatment of optic nerve infiltration by leukemic cells, despite the apparently adequate effect on the other central nervous system manifestations of leukemia. From the anatomic standpoint, this dissociation exists because the optic nerve is in a small bony space, the optic canal. We believe that something acts as a barrier between optic nerve lesions and the remainder of the central nervous system. This barrier may be the massive invasion of leukemic cells, with or without inflammatory swelling of the optic nerve. The barrier intercepts the smooth flow of cerebrospinal fluid between the cranial space and the optic nerve distal to the barrier, so the cytotoxic drugs in the cerebrospinal fluid cannot reach the affected areas of the optic nerve. Such dissociation of therapeutic effect may occur in cases of leukemic involvement of the optic nerve. In Patients 1 and 4, computed tomography showed a swollen optic nerve. This swelling might be caused by invasion of leukemic cells, with or without focal inflammatory swelling. The swollen nerve then fills the optic canal, preventing normal flow of cranial cerebrospinal fluid. In Patient 2, computed tomography showed a normal optic nerve. In this case, either the leukemic cell infiltrate occurred anterior to the lamina cribrosa, or computed tomography was not sensitive enough to demonstrate the swollen optic nerve.

With leukemic involvement of the optic nerve, it is important to treat the optic nerve as well as the remainder of the central nervous system at one time, because the optic nerve is one site of the central nervous system leukemia. The effect of irradiation is uncertain, and not always dramatic. However, this therapy may improve the flow of cerebrospinal fluid between the cranial space and the optic nerve by reducing the number of leukemic cells in the optic canal. This allows the administered cytotoxic drugs to attack the leukemic cells more

TABLE
CLINICAL DATA IN FIVE PATIENTS WITH LEUKEMIC INVOLVEMENT OF OPTIC NERVE*

PATIENT NO., AGE (YRS), SEX	DIAGNOSIS	BONE MARROW FINDINGS AT TIME OF OCULAR INVOLVEMENT	CENTRAL NERVOUS SYSTEM LEUKEMIA	FACIAL NERVE PALSY	COMPUTED TOMOGRAPHY	RADIATION THERAPY
1, 29, F	Acute lymphoblastic leukemia	Complete remission	Proved 1 month before optic nerve involvement	Occurred 2 months before optic nerve involvement	Left optic nerve swelling	Whole brain: 2,600 rad Orbit: 3,600 rad
2, 27, F	Acute myelogenous leukemia	Complete remission	Proved 1 month before optic nerve involvement	Occurred 3 weeks after optic nerve involvement	Normal	Not performed
3, 43, F	Acute myelogenous leukemia	Complete remission	Suspected but not proved	Did not occur	Not performed	Not performed
4, 22, M	Acute myelogenous leukemia	Complete remission	Proved 1 month after optic nerve involvement	Did not occur	Right optic nerve swelling	Whole brain: 1,000 rad Whole spine: 2,000 rad
5, 17, M	Acute lymphoblastic leukemia	Relapse	Suspected but not proved	Did not occur	Not performed	Whole brain: 2,260 rad

*All patients received intrathecal injections of cytarabine, prednisolone, and methotrexate.

effectively and it may reduce the total amount of radiation required.

A combination therapy consisting of irradiation and intrathecal injection of cytotoxic drugs is probably the best available approach for treatment of the optic nerve invasion of leukemia.[8] However, the combined therapy carries a higher risk of leukoencephalopathy. Additionally, antileukemic therapies directed only to the central nervous system and optic nerve often cause a recurrence in the bone marrow. Therefore, this therapy should be combined with appropriate systemic chemotherapy. Good communication and cooperation between ophthalmologists, internists, and radiologists are essential to providing optimal patient care.

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A Long-Term Follow-up Study of Laser Coagulation of Neovascular Membranes in Angioid Streaks

Ö. Gelisken, M.D., F. Hendrikse, M.D., and A. F. Deutman, M.D.

We treated 30 eyes (24 patients) with angioid streaks and neovascular membranes using light coagulation. Of 30 eyes, 16 showed either ameliorated or unchanged visual acuity. Twelve of the remaining 14 eyes retained a visual acuity of 20/200 or better. In 11 patients, the fellow untreated eye showed central macular degeneration with loss of central vision. The follow-up period ranged from two months to 16 years (mean, 3.4 years).

ANGIOID STREAKS, first recognized by Doyne in 1889,[1] are dehiscences in Bruch's membrane. They are usually associated with systemic diseases such as pseudoxanthoma elasticum, Paget's disease, and sickle cell disease. Loss of central vision because of subretinal neovascular membranes is the most serious complication of angioid streaks. Visual disturbances occur with the development of new choroidal vessels together with pigment epithelial damage in the macular area. Consequently, permanent central visual loss appears with recurrent subretinal hemorrhages and fibrous tissue proliferation in the overlying retina. The incidence of macular degeneration in angioid streaks varies from 72%[2] to nearly 100%.[3] This devastating macular degeneration usually occurs bilaterally.

Prophylactic light coagulation of noncomplicated angioid streaks has been suggested,[4] but is generally not recommended. The treatment of complicated angioid streaks with neovascular membranes is still controversial. Some authors have reported unfavorable results,[5-8] while others have had more encouraging experiences.[9-12] Only one of these reports included a long-term follow-up study in a limited group of patients.[12] The purpose of this study was to document the long-term results of light coagulation therapy of complicated angioid streaks.

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Material and Methods

From January 1971 through February 1987, we examined 30 eyes of 24 patients who had disciform reactions associated with angioid streaks as documented by fluorescein angiography. The patients ranged in age from 27 to 74 years (mean, 50 years). The neovascular membranes were treated in one or more sessions by argon or krypton laser, or both. We used a relatively large spot size of 150 to 250 μm, with a power setting of 300 mW and a duration of 0.2 second. In each session the entire membrane was treated. The follow-up period ranged from two months to 16 years (mean, 3.4 years). Fluorescein angiography was performed in all eyes before and after treatment. Eyes that showed recurrences or were incompletely treated were retreated.

Results

Of 30 eyes treated with laser coagulation, 16 (53%) showed either improved or unchanged visual acuity during the follow-up period (Table 1). The other 14 eyes showed a decrease in visual acuity after light coagulation. Twelve of these eyes, however, maintained a useful visual acuity of 20/200 or better.

The follow-up period ranged from two months to 16 years (mean, 3.4 years) after the initial treatment. The treated eyes were divided into four groups according to the length of follow-up period. The posttreatment visual acuity did diminish with increasing length of the follow-up period (Table 2). This is probably because the underlying disease had not been

TABLE 1
CLINICAL FINDINGS IN EYES OF LASER-TREATED PATIENTS

PATIENT NO., AGE (YRS), SEX	EYE	VISUAL ACUITY		FOLLOW-UP (YRS)	LOCATION OF NEOVASCULAR MEMBRANES*	LASER TYPE	NO. OF SESSIONS	DIAGNOSIS OF FELLOW EYE	VISUAL ACUITY IN FELLOW EYE
		PREOPERATIVE	POSTOPERATIVE						
1, 55, F	R	20/200	20/200	4	Macula	Krypton	3	—	—
	L	20/400	20/125	4	Papillomacular bundle	Krypton	2	—	—
2, 47, F	L	20/60	20/200	2	Macula	Krypton	2	Macular degeneration	Counting fingers
3, 70, M	R	20/200	20/40	0.6	Papillomacular bundle	Krypton	2	Macular degeneration	Counting fingers
4, 32, F	R	20/80	20/200	6	Macula	Argon	7	—	—
	L	Counting fingers	20/400	3	Macula	Argon	1	—	—
5, 61, M	R	20/200	20/160	4	Papillomacular bundle	Krypton and argon	1, 2	—	—
	L	20/100	20/200	2.5	Papillomacular bundle	Krypton	4	—	—
6, 54, M	L	Counting fingers	Counting fingers	1	Papillomacular bundle	Argon	3	Angioid streaks	20/20
7, 52, M	L	20/80	20/50	4	Macula	Krypton	4	Angioid streaks	20/25
8, 47, F	L	20/40	20/400	4	Other	Krypton and argon	3, 1	Angioid streaks	20/20
9, 27, F	R	20/50	20/160	0.25	Papillomacular bundle	Krypton	1	Angioid streaks	20/40
10, 60, F	R	20/30	20/30	1.5	Parapapillary region	Krypton	1	Angioid streaks	20/40
11, 38, M	R	20/125	20/100	0.5	Macula	Argon	1	—	—
	L	20/30	20/200	4	Macula	Argon	1	—	—
12, 39, M	R	20/125	20/125	0.25	Macula	Krypton	1	Macular degeneration	Hand motions
13, 59, M	L	20/100	20/200	0.7	Papillomacular bundle	Krypton	2	Macular degeneration	Hand motions
14, 58, M	R	Counting fingers	20/200	4	Macula	Krypton	3	—	—
	L	20/40	20/25	1.5	Other	Krypton and argon	1, 1	—	—
15, 53, F	L	20/160	20/200	2.5	Macula	Krypton	1	Angioid streaks	20/20
16, 41, F	R	20/40	20/200	0.5	Other	Argon	2	Macular degeneration	Hand motions
17, 55, F	L	20/25	20/200	1.5	Macula	Krypton, argon, and krypton	2, 1, 1	Macular degeneration	Counting fingers
18, 38, M	L	20/50	20/80	3	Other	Argon and krypton	1, 2	Macular degeneration	Counting fingers
19, 62, M	R	20/400	20/60	1	Papillomacular bundle	Argon	1	Macular degeneration	Counting fingers
20, 74, M	L	20/60	20/200	7	Parapapillary region	Argon and krypton	1, 2	Macular degeneration	Hand motions
21, 46, F	R	20/60	20/125	0.25	Papillomacular bundle	Krypton	1	Macular degeneration	Counting fingers
22, 51, F	R	Counting fingers	20/40	16	Parapapillary region	Argon	2	—	—
	L	20/16	Counting fingers	16	Macula	Argon	5	—	—
23, 48, M	R	20/40	20/25	0.2	Papillomacular bundle	Krypton	1	Angioid streaks	20/20
24, 40, F	R	20/40	20/40	5	Other	Argon	2	Macular degeneration	Hand motions

*Other, areas other than the macula, papillomacular bundle, and parapapillary region.

TABLE 2
MEAN PREOPERATIVE AND POSTOPERATIVE VISUAL ACUITY BY LENGTH OF FOLLOW-UP

LENGTH OF FOLLOW-UP	NO. OF EYES	VISUAL ACUITY	
		PREOPERATIVE	POSTOPERATIVE
0 to 1 yrs	8	20/60	20/60
1 to 3 yrs	8	20/60	20/60
3 to 5 yrs	9	20/80	20/125
>5 yrs	5	20/50	20/80

TABLE 3
MEAN VISUAL ACUITY BY LOCATION OF NEOVASCULAR MEMBRANES

LOCATION OF NEOVASCULAR MEMBRANES	NO. OF EYES	VISUAL ACUITY	
		PREOPERATIVE	POSTOPERATIVE
Parapapillary region	3	20/60	20/50
Papillomacular bundle	10	20/100	20/80
Macula	12	20/60	20/160
Other	5	20/40	20/60

eliminated. There is still a high probability of recurrence and new neovascular membranes, as noted in our cases (Figure). However, after a follow-up period of five years or more, 50% of the initial mean visual acuity was preserved (Table 2). This suggests that the treatment was beneficial.

The eyes were also grouped according to location of the neovascular membrane before treatment (Table 3). The neovascular membrane was localized in the peripapillary region in three eyes, in the papillomacular bundle in ten eyes, in the macular region at a distance of not more than 1/8 disk diameter to the avascular zone in 12 eyes, and in more than one locus in five eyes. Eyes in which the primary neovascular membranes were located in the parapapillary and papillomacular regions responded best to treatment. Eyes that had lesions in the macula or multifocal lesions had the worst posttreatment prognosis.

All eyes had bilateral angioid streaks. In 11 patients, the fellow eyes showed disciform macular degeneration in a scar stage, with visual acuity less than or equal to counting fingers at 1 m and a loss of central vision. Ten of these 11 patients noted a rapid deterioration of their sight in the untreated eye. The treated eyes of these patients had a visual acuity ranging from 20/40 to 20/200 (mean, 20/100) after a follow-up of two months to seven years (mean, two years). In this group, the treated eyes maintained useful visual acuity during the follow-up period as opposed to the untreated eyes. It is still uncertain, however, whether these eyes will preserve their visual acuity. Six patients showed bilateral involvement and have all been treated. The fellow eyes in the remaining seven patients did not show any leakage of neovascular membranes during the follow-up period.

Neovascular membranes in angioid streaks usually occur during middle age. When the success rate was correlated with age, we found that the best posttreatment results occurred in patients aged 60 years or more (Table 1). This finding is in contrast with clinical experience in age-related and juvenile macular disciform reactions. However, in the five patients aged 60 years or more, three had neovascular membranes in the parapapillary region and two had membranes in the papillomacular region.

Twenty of the 30 eyes required two or more treatment sessions (Figure). The ten eyes in which only one treatment has been performed have had a shorter follow-up period (mean, 1.3 years) than the other eyes (mean, 4.4 years). Intensive follow-up and patient instruction is necessary since the recurrence rate and possibility of incomplete treatment is high. Recurrences that occur within several weeks of treatment and incompletely treated neovascular membranes should be retreated immediately.

Discussion

We did not notice a significant clinical difference between eyes that received argon laser treatment and those that received krypton laser treatment. However, krypton laser should be the treatment of choice for neovascular membranes in the parapapillary and macular regions.

This long-term follow-up study showed that treatment of neovascular membranes in angioid streaks produces satisfactory visual results as well as regression of the neovascularizations. The treated eyes maintained a usable visual acuity for at least a longer period than

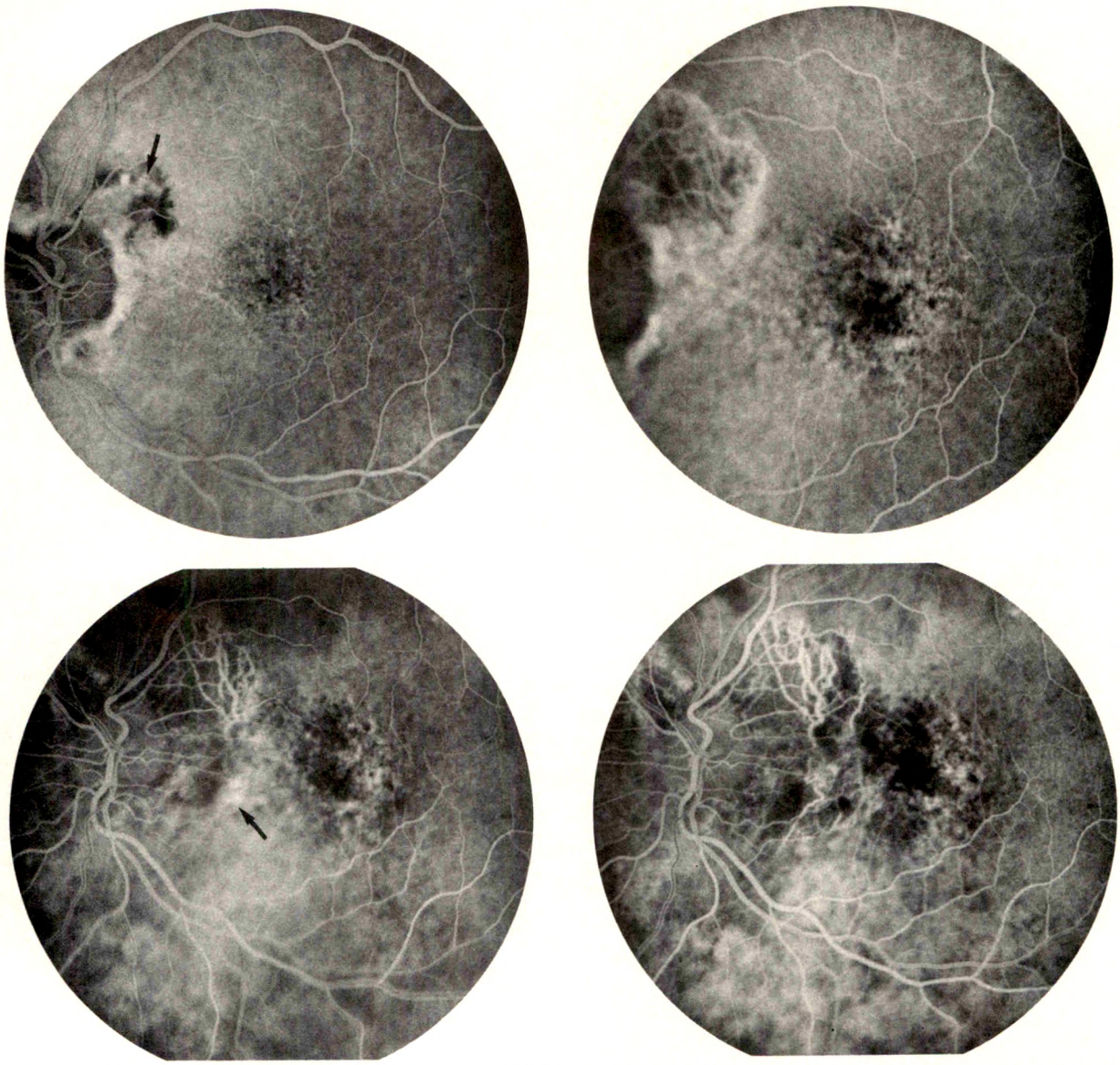


Figure (Gelisken, Hendrikse, and Deutman). Patient 20. Top left, Neovascular membrane before treatment (arrow); visual acuity, 20/60. Top right, Two years after the first treatment; visual acuity, 20/50. Bottom left, Recurrence of neovascular membrane three years after the first treatment (arrow); visual acuity, 20/200. Bottom right, Ten months after second treatment; visual acuity, 20/200.

the untreated fellow eyes. The untreated fellow eyes all suffered a loss of central vision within a short time (Table 1). For successful treatment the eyes should be treated as early as possible. The neovascular membranes should be treated completely and adequately in order not to stimulate further neovascularization.[6,13] Paracentral (in the avascular zone) and subfoveal neovascular membranes should probably not be treated.

Although a double-masked, randomized trial would allow more definite conclusions, in this relatively rare ocular disease, a long-term controlled study can only be performed as a multicenter trial.

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OPHTHALMIC MINIATURE

Within four walls, probably few of us will recognize *thalamus* as meaning an inner room, a reminder that the eye was once regarded as the outer chamber of sight. Furnish the room with a hearth to get *focus* and with *cline* a bed for clinic and its many derivatives. On the hearth a fire blazes and the skillet of porridge is sluggishly boiling. The gruel within is *atheros*, in appearance and consistency sufficiently like to give its name to *atheroma* the porridge tumour.

G. P. Crookes, *Ophthalmologica*
Trans. Ophthalmol. Soc. U.K. 84:259, 1964

Fadenoperation for the Management of Complicated Incomitant Vertical Strabismus

Edward G. Buckley, M.D., and Bettina B. Meekins, M.D.

We reviewed retrospectively the records of 17 patients with incomitant vertical diplopia secondary to an underacting inferior rectus muscle who had been treated by surgically weakening the contralateral inferior rectus muscle with a posterior fixation suture (fadenoperation). This was the sole procedure in four patients with blowout fractures and in two patients with restriction secondary to scleral buckling procedures. It was combined with horizontal or vertical muscle surgery in 11 patients. The procedure was particularly useful in preventing diplopia on downgaze after excessive weakening of a tight inferior rectus muscle in seven patients with thyroid ophthalmopathy. In three patients it was used in anticipation of an iatrogenic incomitancy in downgaze secondary to a large recession of a tight inferior rectus muscle. All patients were markedly improved after surgery and no complications were encountered.

THE FADENOPERATION, introduced by Cüppers in 1976,[1] involves suturing the rectus muscle belly to the sclera at least 1 cm posterior to its normal anatomic insertion. This results in selective weakening of the muscle in its field of action, without changing ocular alignment in the primary gaze position. The indications for the fadenoperation have been well described.[2-11] They include dissociated vertical deviation, nystagmus blockage syndrome, double elevator palsy, convergence esotropia, hypertropias associated with adduction in Duane's syndrome, and congenital nystagmus with a head turn. Saunders[5] reported successful elimination of vertical diplopia after a fadenoperation of the nonparetic inferior rectus muscle in three patients with blowout fractures and muscle entrapment. He generated a mild limitation of depression in the normal eye, thereby balancing rotational forces and eliminating acquired vertical strabimus in downgaze.

We report the results of 17 fadenoperations performed on nonparetic contralateral inferior rectus muscles for incomitant vertical strabismus secondary to a variety of conditions, including thyroid ophthalmopathy, blowout fractures, and scleral buckling procedures, as well as the results in three patients who underwent the fadenoperation in anticipation of an iatrogenic vertical incomitancy in downgaze.

Material and Methods

We reviewed retrospectively 17 consecutive fadenoperations performed between 1983 and 1985. There were nine men and eight women, with an average age of 48 years (range, 27 to 70 years). Each patient had evidence of inferior rectus muscle paresis or restriction preoperatively or was anticipated to have a weakness postoperatively secondary to a maximal inferior rectus muscle recession. Seven patients had orbital blowout fractures, six patients had thyroid ophthalmopathy, two patients had undergone retinal detachment surgery that involved placement of a silicone encircling band and buckle, one patient had undergone a Krönlein procedure for Wegener's granulomatosis, and one patient was status-post left inferior oblique muscle recession (Table).

Before surgery, all patients underwent a detailed ophthalmic examination, including a comprehensive motility examination with sensory evaluation, motility measurements in all nine cardinal fields of gaze, forced ductions, and diplopia fields. All surgery had been performed by one of us (E.G.B.). The technique consisted of isolation of the inferior rectus muscle of the freely moving eye through a von Noorden fornix-based conjunctival flap. With

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the muscle secured and elevated on a Jameson muscle hook, all check ligaments and intermuscular septa were meticulously dissected free several millimeters posterior to the exit of the vortex veins. With the muscle on stretch, two fibrobraided 5-0 polyester sutures on spatulated needles were used to secure the muscle to the globe. Each suture was passed through partial-thickness sclera perpendicular to the long axis of the muscle an average of 13 mm posterior to the muscle insertion site, incorporating the lateral one third of the muscle belly. The presence of the vortex vein limited the posterior extent of suture placement in each case. The conjunctiva was closed with an interrupted perilimbal wing suture of 8-0 polyglactin. The fadenoperation was combined with other strabismus procedures in 11 patients. Four of the patients had horizontal muscle surgery, four had horizontal or vertical surgery, or both, and three had previous vertical muscle surgery. One patient underwent a marginal myotomy before the placement of the posterior fixation suture. In three patients, the fadenoperation was performed in anticipation of contralateral inferior rectus weakening after maximal inferior rectus muscle recession procedures. No attempt was made to vary the effect of the fadenoperation by placing the suture at various distances from the insertion; each patient had the posterior fixation suture placed just anterior to the vortex vein.

Case Reports

Case 1

A 28-year-old man had been struck in the right orbit with an ax handle four years before our examination. At that time orbital x-rays showed a right orbital fracture. The patient remained asymptomatic until four years later when he was involved in a bicycle accident in which he struck his right orbit on the bicycle mirror, and sustained a laceration of the right upper eyelid and inferior canaliculus. Orbital x-rays failed to demonstrate definite evidence of a floor fracture. One week after surgical repair of his lacerations, the patient complained of vertical diplopia. After four months, he still experienced diplopia and was referred to us for further examination.

Our examination showed 3 prism diopters of right hyperphoria at distance and near, with excellent fusion in the primary position. On downgaze, the deviation increased to 25 prism diopters of right hypertropia. No enophthalmos was present, but there was limitation of depression of the right eye (Fig. 1). Results of the rest of the ocular examination were normal. Binocular diplopia fields showed that diplopia occurred when downgaze exceeded 10 degrees. Results of the remainder of the examination were normal. Computed tomography of the orbits with coronal reconstructions showed fractures of the right medial orbital wall, with displacement of the lamina papyracea but without medial rectus muscle entrapment. A nondisplaced fracture of the right orbital floor was present, with no evidence of herniated orbital contents. However, the inferior rectus muscle appeared enlarged.

Five months after injury, the patient underwent a fadenoperation of the left inferior rectus muscle, with placement of the sutures 13 mm posterior to the muscle insertion site. No other strabismus procedures were performed.

Postoperatively the patient was orthophoric in the primary position at distance and near, with only 1 or 2 prism diopters of left hypertropia in extreme downgaze (Fig. 1). Binocular diplopia fields showed marked improvement in the range of single vision, with only a small island of diplopia remaining 40 degrees below the horizontal meridian. The patient has remained asymptomatic for 19 months.

Case 12

A 65-year-old woman with Graves' ophthalmopathy was referred because of strabismus. Three years before our examination the patient was found to have hyperthyroidism. She was treated with radioactive iodine and hypothyroidism developed. She has since received thyroid hormone replacement to maintain a euthyroid state. Two years before our examination the patient began to experience horizontal and vertical diplopia. At that time visual acuity was 20/20 in both eyes. Ocular motility showed a 30-prism diopter left hypertropia and 45 prism diopters of esotropia at 20 feet. At 13 inches, 30 prism diopters of left hypertropia and 20 prism diopters of esotropia were present. Field measurements showed the following: on dextroversion, there were 30 prism diopters of esotropia and 40 prism diopters of left hypertropia; on supraduction, 40 prism diopters of left hypertropia; on infraduction, 10 prism diopters of left hypertropia and 10 prism diopters of esotropia; and on levoversion, 10 prism diopters of left hyper-

TABLE

SUMMARY OF DATA ON 17 PATIENTS UNDERGOING INFERIOR RECTUS FADENOPERATION

PATIENT NO., AGE (YRS), SEX	DIAGNOSIS	AMOUNT OF DEVIATION (△)				SURGERY	LENGTH OF FOLLOW-UP (MOS)
		PREOPERATIVE		POSTOPERATIVE			
		PRIMARY	DOWNGAZE	PRIMARY	DOWNGAZE		
1, 28, M	Blowout fracture	3 △ right hyperphoria	25 △ right hypertropia	Orthophoria	2 △ left hypertropia	Left inferior rectus muscle fadenoperation	19
2, 36, M	Blowout fracture	Orthophoria	12 △ right hypertropia	Orthophoria	Orthophoria	Left inferior rectus muscle fadenoperation	27
3, 53, F	Blowout fracture	3 △ right hyperphoria	10 △ right hypertropia	Orthophoria	Orthophoria	Left inferior rectus muscle fadenoperation	15
4, 55, M	Blowout fracture	4 △ intermittent right hypertropia, 20 △ esotropia	14 △ right hypertropia, 10 △ esotropia	Orthophoria	Orthophoria	Left inferior rectus muscle fadenoperation, right medial rectus muscle adjustable recession	14
5, 27, F	Blowout fracture	10 △ left hypertropia	Orthophoria	Orthophoria	4 △ right intermittent hypertropia	Left inferior rectus muscle fadenoperation, right inferior rectus muscle adjustable recession	16
6, 65, M	Blowout fracture	1 △ exophoria	15 △ right hypertropia	Orthophoria	Orthophoria	Left inferior rectus muscle fadenoperation	12
7, 45, M	Blowout fracture	10 △ right hypertropia, 15 △ esotropia	10 △ left hypertropia, 10 △ esotropia	Orthophoria	3 △ left intermittent hypertropia	Right inferior rectus muscle fadenoperation, right superior rectus muscle adjustable recession, left medial rectus muscle adjustable recession	12
8, 60, M	Thyroid	Orthophoria	20 △ right hypertropia	Orthophoria	5 △ right intermittent hypertropia	Left inferior rectus muscle fadenoperation (previously: right inferior rectus muscle adjustable recession)	21
9, 58, M	Thyroid	10 △ esotropia	8 △ left hypertropia, 12 △ esotropia	Orthophoria	Orthophoria	Right inferior rectus muscle fadenoperation, right medial rectus muscle adjustable recession	22
10, 34, F	Thyroid	20 △ left hypertropia, 5 △ esotropia	Orthophoria	5 △ intermittent esotropia	Orthophoria	Left inferior rectus muscle fadenoperation, right inferior rectus muscle adjustable recession	13
11, 43, F	Thyroid	10 △ right hypertropia, 10 △ exotropia	20 △ right hypertropia, 15 △ exotropia	2 △ right intermittent hypertropia, 4 △ intermittent exotropia	2 △ right intermittent hypertropia, 5 △ intermittent exotropia	Left inferior rectus muscle fadenoperation, left medial rectus muscle adjustable recession (previously: right inferior rectus muscle recession, right superior rectus muscle adjustable recession)	20

TABLE *(Continued)*

PATIENT NO., AGE (YRS), SEX	DIAGNOSIS	AMOUNT OF DEVIATION (△) PREOPERATIVE PRIMARY	PREOPERATIVE DOWNGAZE	POSTOPERATIVE PRIMARY	POSTOPERATIVE DOWNGAZE	SURGERY	LENGTH OF FOLLOW-UP (MOS)
12, 65, F	Thyroid	30 △ left hypertropia, 45 △ esotropia	10 △ left hypertropia, 15 △ esotropia	5 △ intermittent exotropia	10 △ intermittent exotropia	Bimedial rectus muscle adjustable recessions, right inferior rectus muscle adjustable recession, left inferior rectus muscle fadenoperation	9
13, 60, F	Thyroid	Orthophoria	20 △ right hypertropia	Orthophoria	4 △ right hyperphoria	Left inferior rectus muscle fadenoperation (previously: right inferior rectus muscle adjustable recession)	12
14, 60, M	Wegener's granulomatosis	5 △ right hypertropia, 10 △ exotropia	20 △ right hypertropia, 10 △ exotropia	Orthophoria	Orthophoria	Left inferior rectus muscle fadenoperation, right lateral rectus muscle adjustable recession	19
15, 72, F	Scleral buckle of the left eye	3 △ left hypertropia	18 △ left hypertropia, 6 △ exotropia	Orthophoria	4 △ intermittent exotropia	Right inferior rectus muscle fadenoperation with marginal myotomy	24
16, 65, M	Scleral buckle of the right eye	Orthophoria	15 △ right hypertropia	Orthophoria	4 △ right intermittent hypertropia	Left inferior rectus muscle fadenoperation	30
17, 51, M	Left superior oblique muscle palsy	4 △ left intermittent hypertropia	10 △ left hypertropia	Orthophoria	Orthophoria	Right inferior rectus muscle fadenoperation (previously: left inferior oblique muscle recession)	16

tropia and 40 prism diopters of esotropia (Fig. 2). During a one-year follow-up period, the ocular motility measurements remained stable. The patient underwent a bimedial rectus muscle recession using adjustable sutures, a right inferior rectus muscle recession with adjustable sutures, and a left inferior rectus muscle fadenoperation. Postoperatively, the patient was found to have an intermittent exotropia of 5 prism diopters at distance and 10 prism diopters at near. On extreme right gaze, she had 20 prism diopters of exotropia and on upgaze 10 prism diopters of left hypertropia (Fig. 3). She had a mild weakness of the right medial rectus muscle secondary to a maximal recession. Nine months after her first operation, she underwent a small left lateral rectus muscle recession with posterior fixation suture. Three months postoperatively, she had a 10-prism diopter left hypertropia on extreme upgaze but was otherwise free of diplopia.

Case 13

A 60-year-old woman with thyroid ophthalmopathy developed restriction of the right inferior rectus muscle resulting in 40 prism diopters of left hypertropia in the primary position at distance and near. The deviation increased significantly on upgaze but was eliminated on downgaze. During a one-year follow-up period, there was no change in her ocular motility measurements. She underwent a recession of the right inferior rectus muscle on an adjustable suture. Postoperatively, the patient was

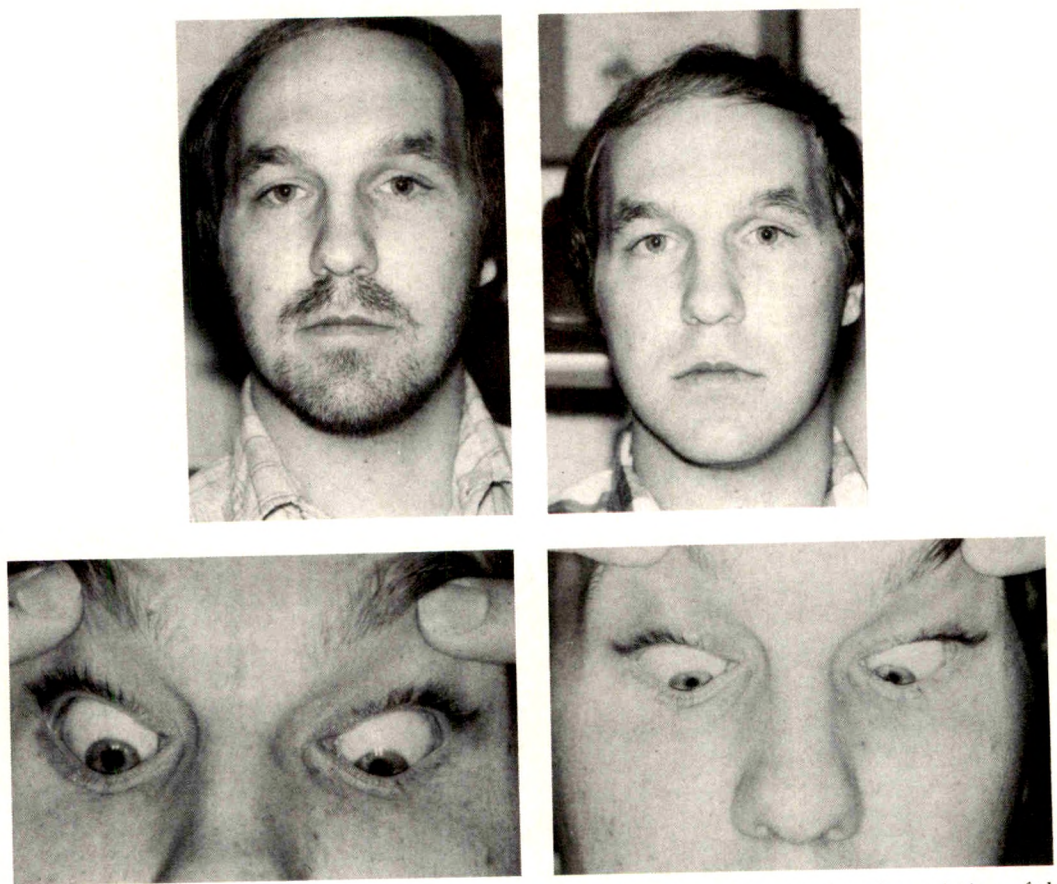


Fig. 1 (Buckley and Meekins). Case 1. Left, Preoperatively, primary position (top) and restriction of the right inferior rectus muscle on downgaze (bottom). Right, Postoperatively, primary (top) and downgaze (bottom) positions.

orthophoric in the primary position at distance and near, with 20 prism diopters of right hypertropia on downgaze (Fig. 4). In an effort to eliminate diplopia on downgaze, a 13-mm fadenoperation was performed on the left inferior rectus muscle. Postoperatively, the patient remained orthophoric in the primary position, with a residual hyperphoria of 4 prism diopters in extreme downgaze (Fig. 4). The patient has remained free of diplopia for 12 months.

Case 15

A 69-year-old woman developed a rhegmatogenous retinal detachment in the left eye extending clockwise from the 4 o'clock to the 2 o'clock meridians, sparing the macula. This was successfully repaired with a 2.5-mm encircling band supplemented with a 9-mm silicone tire placed over the retinal breaks identified in the superonasal quadrant. Postoperatively, the patient noted vertical diplopia. In the primary position, field measurements disclosed 3 prism diopters of left hypertropia at distance and 4 prism diopters of left hypertropia at near. This increased in downgaze to 18 prism diopters of left hypertropia and 6 prism diopters of exotropia (Fig. 5). The forced duction test was positive and the deviation was felt to be secondary to restriction of the left superior rectus muscle by the exoplants. To obviate removal of the exoplants, a 15-mm fadenoperation combined with a marginal myotomy was performed on the right inferior rectus muscle. Postoperatively, she experienced complete resolution of her left hypertropia and vertical diplopia (Fig. 5). This has remained stable for 24 months after surgery.

Results

Seventeen patients with incomitant vertical strabismus and associated vertical diplopia were treated with fadenoperations of the contralateral nonparetic inferior rectus muscle. This was combined with other conventional strabismus procedures in ten patients. The su-



Fig. 2 (Buckley and Meekins). Case 12. Preoperative ocular motility in patient with ophthalmopathy. Note marked restriction of the inferior rectus muscle on the right.

tures were placed an average of 13 mm (range, 12 to 15 mm) posterior to the muscle insertion site. Diplopia was improved or eliminated in all patients. Nine patients were orthophoric in downgaze (Table).

In our series, the effectiveness of the fadenoperation seemed to be independent of the magnitude of the deviation in downgaze. Both large and small deviations were virtually eliminated by placement of the posterior fixation suture at the same location.

Patient 8, a patient with thyroid ophthalmopathy and a tight inferior rectus muscle, was initially fusing in downgaze, with marked diplopia in the primary position. The patient underwent a right inferior rectus muscle recession, with a resultant duction lag of that eye on downgaze. He subsequently underwent a fadenoperation on the contralateral inferior rectus muscle, thereby eliminating his iatrogenically induced diplopia on downgaze. Patients 5, 10, and 12 were treated with a fadenoperation on the contralateral inferior rectus muscle on the assumption that a maximum inferior rectus muscle recession would result in vertical diplopia on downgaze. These patients all did well postoperatively. Patient 5 had 4 prism diopters of intermittent right hypertropia, and Patients 10 and 12 had no vertical deviation on downgaze.

No complications occurred in any of these patients. In particular, examination of the fundi while the pupil was dilated showed no abnormalities in the area of the placement of the posterior fixation sutures.

Discussion

In theory, the best indication for the fadenoperation is incomitant strabismus in which the maximum ocular deviation is away from the primary position. The effect of the fadenoperation is to create a progressive loss of pull or torque as the muscle moves further into its field of action. As such, it can be used in situations where yoke muscles are unbalanced. It is especially useful when further surgery on the weaker yoke muscle is contraindicated. The



Fig. 3 (Buckley and Meekins). Case 12. Postoperatively, note minimal limitation of the right inferior rectus muscle, even though it has been recessed 10 mm. Exotropia on left gaze is secondary to maximum recession of the right medial rectus muscle.

best example of this is in patients with orbital blowout fractures who have a vertical incomitancy on downgaze secondary to a weak or tethered inferior rectus muscle. Because these patients have no deviation in the primary position, further surgery on the offending inferior rectus muscle can only jeopardize this situation. As Saunders[5] has shown, placement of a posterior fixation suture on the normal contralateral inferior rectus muscle can create a graded limitation of depression in that eye, thereby balancing rotational forces and eliminating vertical diplopia. Our results confirm his findings in four patients with blowout fractures whose only deviation was in downgaze.

There are other situations in which muscle surgery on the restricted eye is potentially hazardous, not only because of possible disruption of ocular alignment in the primary position, but because of the risks associated with this type of surgery in eyes with other disease. Examples include patients who have had encircling silicon bands or scleral buckles placed as part of a retinal detachment repair, and patients with orbital tumors. Patients 15 and 16 both had undergone extensive retinal detachment surgery with placement of large scleral buckles before developing diplopia. These patients had little deviation in the primary position but demonstrated marked restriction of the previously operated on eye on downgaze. By directing attention to the contralateral overacting yoke muscle (in this case, the inferior rectus muscle), satisfactory results can be obtained relatively easily.

The fadenoperation can also be used to eliminate or prevent an iatrogenic incomitant vertical strabismus after maximum contralateral inferior rectus muscle recession, as demonstrated in Cases 5, 8, 10, 12, and 13. In these cases a tight, poorly functioning inferior rectus muscle was recessed in order to return the eye to the primary position. In Case 8, the patient had a large right hypertropia on downgaze postoperatively. Subsequent fadenoperation of the normal left inferior rectus muscle balanced the rotational forces in downgaze and eliminated diplopia. Cases 5, 10, and 12 had fadenoperations placed at the time of the inferior rectus muscle recession surgery in anticipation

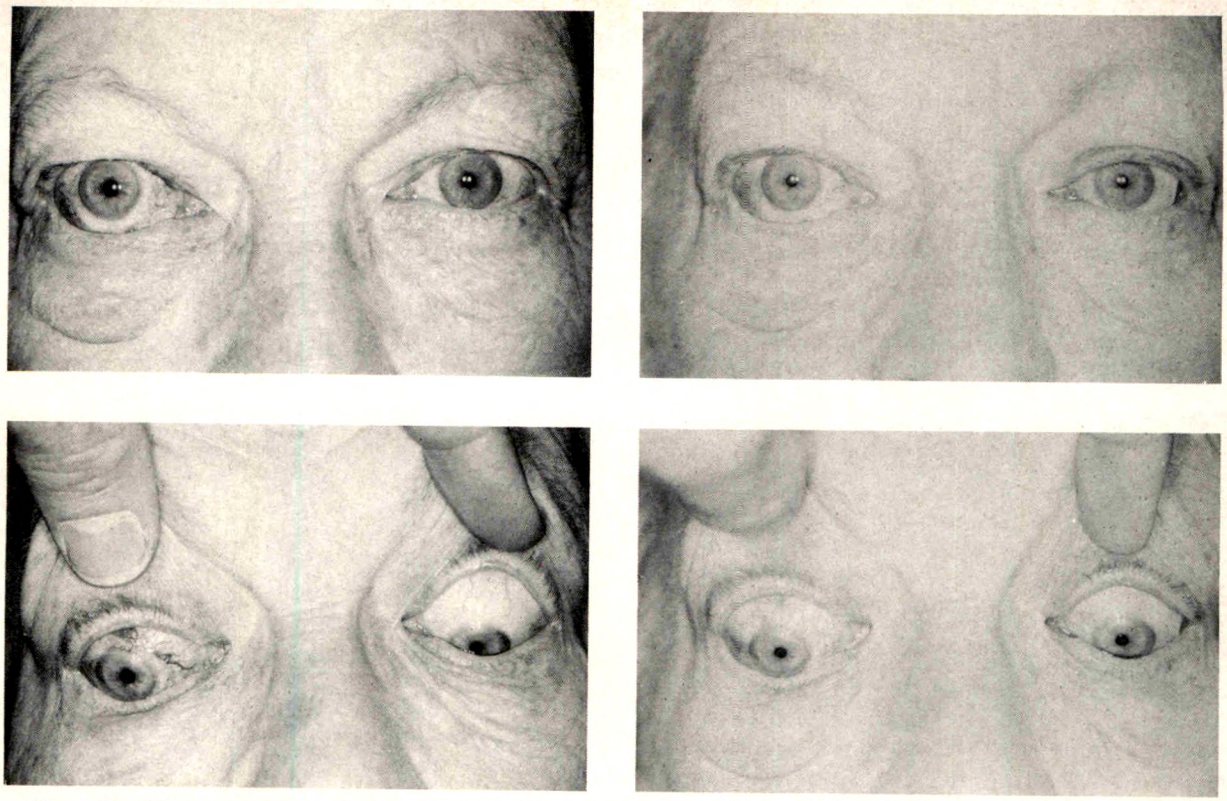


Fig. 4 (Buckley and Meekins). Case 13. Left, Preoperatively, note limitation of inferior rectus muscle on the right eye secondary to a large recession in the primary (top) and downgaze (bottom) positions. Right, Postoperatively, downgaze vertical incomitancy is eliminated by left inferior rectus muscle fadenoperation.



Fig. 5 (Buckley and Meekins). Case 15. Left, Preoperatively, note limitation of the left eye on downgaze. Right, Postoperative motility showing normal versions on downgaze.

of an infraduction deficit after maximal inferior rectus muscle recession. This had two major advantages. First, it eliminated the need for subsequent surgery. Second, it simplified the determination of how much postoperative adjustment to perform on the contralateral, previously restricted inferior rectus muscle. Often, the surgeon is faced with the dilemma of how much recession to perform in order to return the eye to the primary position, yet not weaken the muscle so much so that downgaze is affected. We found it much easier to preserve downgaze function when the relatively normal contralateral inferior rectus muscle was restricted by the posterior fixation suture. In all of our cases we were able to preserve enough downgaze function to allow the patient to use bifocals without difficulty.

A surprising finding was that the effectiveness of identical fadenoperations appeared to be similar for widely different magnitudes of deviation in downgaze. It has been recommended that the suture be placed at least 11 mm posterior to the muscle insertion site.[6] In our series, the sutures were placed just anterior to the location of the vortex vein, which was found to be an average of 13 mm posterior to the muscle insertion site. No attempt was made to adjust the distance that the suture was placed posteriorly based on the preoperative deviation. As can be seen in the Table, the deviation was eliminated irrespective of its initial magnitude.

Selective weakening of a muscle only in its field of action without changing alignment in the primary position is only one advantage of the fadenoperation. In addition, it rarely causes clinically significant limitation of ductions and is theoretically reversible if nonreactive sutures are used.[9] Alio and associates[9] demonstrated the potential reversibility of the procedure when they examined histopathologically 20 eyes in which fadenoperations had been performed on the superior rectus muscle of albino rabbits. Findings included granuloma foreign body reaction around the sutures, collagenization of the muscle tissue after the first postoperative month, and degeneration of muscle fibers. After the third postoperative month, the procedure is probably not reversible because of fibrotic changes and muscle fiber degeneration.

No complications were encountered in our series of 17 patients. Complications have been reported in the literature, however.[2,3,11] The most common postoperative complication is undercorrection secondary to inadequate posterior placement of sutures, loose sutures, or anterior migration of sutures.[3] Other complications are more likely related to poor intraoperative exposure. Alio and Faci[11] retrospectively reported chorioretinal scars underlying sutures in 28 of 187 eyes (15.0%). One case of choroidal ischemia after a fadenoperation was reported. Other unusual and rare complications include isolated reports of persistent mydriasis, optic atrophy, macular edema, vitreous hemorrhage, and choroidal detachments (unpublished data). With careful intraoperative technique, most complications can be avoided.

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Negative Antibody Response to Long-Term Treatment of Facial Spasm With Botulinum Toxin

Russell S. Gonnering, M.D.

Over a period of 163 weeks, 223 injections of botulinum A toxin were administered to 38 patients with facial spasm syndromes. The maximum cumulative toxin dose was 553 units, the maximum number of injections in any given patient was 16, and the maximum dosage of any given injection was 52.5 units. Sera from these patients showed no antibody production when measured with a standard mouse lethality bioassay.

BOTULINUM A TOXIN has proved useful in the treatment of essential blepharospasm, Meige's syndrome, and hemifacial spasm.[1-12] Although this protein can elicit a humoral antibody response, Biglan and associates[13] reported an absence of such a response in 28 patients treated with clinical doses of toxin. In that study, the maximum cumulative toxin dose was 125 units, with a maximum of five injections. The longest duration of treatment before serum sampling was 36 weeks.

Greene and associates[14] have recently reported that clinical production of antibodies occurs in some patients treated for spasmodic torticollis with significantly larger toxin doses than that used in the treatment of facial spasm. The present study was undertaken in an attempt to define a possible dose/response curve for production of antibodies in response to long-term treatment with botulinum toxin in the dosage range commonly used in facial spasm.

Patients and Methods

Serum samples were collected from 38 patients (27 women and 11 men) and subjected to a standard mouse lethality bioassay for the presence of antitoxin.[15] Nineteen patients had essential blepharospasm, 11 had hemifacial spasm, and eight had Meige's syndrome. A total of 223 injections were given to these patients over a 163-week period. The mean cumulative dose was 148.2 units, with a maximum cumlative dose of 553.0 units (Table 1). The mean treatment duration was 98.8 weeks, with a mean of 5.9 injections given per patient. The mean dosage per injection ranged from 14.1 units in hemifacial spasm to 31.3 units in Meige syndrome (Table 2). The length of relief of symptoms per injection ranged from a mean of 10.3 weeks in Meige syndrome to 15.0 weeks in hemifacial spasm.

Results

No antibodies to botulinum A toxin were seen in any of the serum samples studied. This indicates that less than 0.001 international unit of antitoxin was present per milliliter of sera.

Discussion

The finding of Greene and associates[14] of serum antibodies in patients treated with botulinum A toxin has potentially serious clinical implications. In treating spasmodic torticollis, they used significantly higher doses (mean, 208 units; range, 90 to 413 units) than that used in the treatment of facial spasm. Development of antibodies to the toxin would be expected to cause resistance to further treatment, as Scott[16] found the toxin to be ineffective in a monkey immunized beforehand with botulinum toxoid.

In clinical immunization against a microbial toxin, the detoxified toxin, or toxoid, is normally used to avoid clinical disease.[17] This presents a large concentration of antigenic determinants of the toxin, without most of the attendant

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TABLE 1
CUMULATIVE DATA ON 38 PATIENTS TREATED WITH BOTULINUM A TOXIN

	MEAN	S.E.M.	MINIMUM VALUE	MAXIMUM VALUE
Cumulative dose (units) per patient	148.2	20.0	12.5	553.0
Treatment duration (wks)	98.8	6.9	4.0	163.0
No. of injections per patient	5.9	0.6	1	16

risks of toxin injection itself. Concentration of antigenic function of a toxoid is normally given in flocculation units, determined according to the Ramon procedure.[18] In this procedure, known concentrations of antitoxin are incubated with the unknown toxoid in a water bath at 44 to 46 C. The mixture that flocculates first is approximately neutral, with no toxoid or antitoxin excess. This unit of antigenic activity, the L_f dose, is calculated as follows:

$$L_f/\text{ml toxoid} = \frac{\text{antitoxin units/ml} \times \text{ml of antitoxin}}{\text{ml of toxoid}}.$$

Standard pentavalent botulinum toxoid at the Centers for Disease Control contains 1.7 L_f of type A antigen per milliliter (oral communication, Charles L. Hatheway, Ph.D., December 1987). This corresponds to approximately 16.25 μg of type A antigen per milliliter. Normal immunization schedules call for administration of 0.5 ml of toxoid (812.5 ng of type A antigen) at weeks 0, 2, 12, and 52.

TABLE 2
TOXIN DOSE AND RESPONSE PER INJECTION

	MEAN	S.E.M.	MINIMUM VALUE	MAXIMUM VALUE
Toxin dose per injection (units)				
Blepharospasm	26.1	0.5	12.5	45.0
Hemifacial spasm	14.1	0.4	10.0	20.0
Meige's syndrome	31.3	1.6	10.0	52.5
Total	25.4	0.7	10.0	52.5
Response per injection (wks)				
Blepharospasm	10.9	0.4	1.0	32
Hemifacial spasm	15.0	0.4	9.0	20
Meige's syndrome	10.3	0.7	1.0	25
Total	11.5	0.3	1.0	32

Using the same concentration of antigen, but with a zero-, two-, ten-, and 52-week schedule, Fiock, Cardella, and Gearinger[19] found detectable serum type A antitoxin levels in 65% of patients at 12 weeks, and in 100% of patients at 60 weeks.

In contrast to toxoid, botulinum toxin is measured in units of biologic activity. One unit is equivalent to the LD_{50} dose for 18- to 20-g female Swiss Webster mice, and is approximately 0.4 ng.[3] In this study, the mean toxin dose was 25.4 units (10.15 ng) with a range of 10 to 52.5 units (5 to 21 ng). The highest dose reported by Greene and associates[14] was 413 units (165.2 ng). The maximum cumulative dose in this study was 553 units (221.2 ng) given over a 159-week period.

It would therefore appear that the immunogenic dose of botulinum A toxin administered clinically is between 52.5 and 413 units, which seems to be well below the antigenic load contained in botulinum toxoid. Fiock, Cardella, and Gearinger[19] have pointed out, however, that different toxins can have the same L_f value (antigenicity) but differing LD_{50} values (biologic activity). In such situations, partial detoxification of the toxin is presumed to have taken place. If a similar process occurs during the initial preparation of the botulinum A toxin, a much higher antigenic load is possible than that calculated on the basis of LD_{50} data alone (oral communication, Charles L. Hatheway, Ph.D., December 1987).

It seems unlikely that subsequent development of antibodies to the toxin will occur in the doses reported in this study for treatment of facial spasm. Effective duration of relief of symptoms with this dosage is comparable to that seen in other studies using higher dosages. As the development of antibodies to the toxin will preclude its further usefulness in those patients, it seems prudent to use the lowest possible effective dose.

The minimum dose and injection schedule required to induce antibody formation is still not known. This information will prove important in formulating a rational treatment protocol for treatment of such diseases as spasmodic torticollis, where a high toxin dosage appears to be needed.

ACKNOWLEDGMENT

The botulinum A toxin used in this study, Oculinum, was provided by A. B. Scott, M.D., the Smith-Kettlewell Eye Research Founda-

tion, San Francisco, California. Charles L. Hatheway, Ph.D., performed the mouse lethality bioassay at the Centers for Disease Control.

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EDITORIAL

The Oral Examinations of the American Board of Ophthalmology and the Appointment Panel System

Ronald M. Burde and William H. Spencer

At the oral examination held in San Francisco in the fall of 1986, the American Board of Ophthalmology introduced "examination by appointment." All ophthalmologists who were certified before this time have memories of their own oral examinations and recall the experience as a lengthy "rite of passage." The structure of that examination required candidates to spend several days in the city in which the examinations were held, as a maximum of three subjects were tested in any one day, and to wait in so-called "pool" rooms until an examiner was available, at which time they were summoned to be tested. The duration of the examination in each subject, although designed to last approximately one-half hour, was inconsistent, and candidates who responded slowly often underwent extensive testing. On many occasions it was difficult for the examiner to ask a sufficient number of questions to assess the breadth of a candidate's knowledge in a given subject. Although these examinations were always conducted in a professional and fair fashion, the Board was aware of their imperfections. Following the institution of examination by appointment, comments from both candidates and associate examiners were very positive.

In the spring of 1987 the American Board of Ophthalmology introduced an examination conducted by appointment within a Panel System. This system is designed not only to benefit candidate schedules by limiting the time of the examination to a one-half day period but also to improve the validity and the fairness of the oral examination process. The purpose of this editorial is to introduce and explain the Panel System to all American Board of Ophthalmology diplomates as well as to current and future candidates.

At present each candidate is assigned to one of 17 panels, each composed of six associate examiners and one Board director. In the one-half day time, each candidate is examined for a period of 25 minutes in each of six subjects with a 15-minute break midway in the examination period. Prescreening ensures that all candidates are unknown to the examiners, and each panel includes candidates whose grades on the written qualifying examination varied from high to low. To promote consistency, all associate examiners in each subject (category) meet beforehand with the Board director responsible for overseeing the questions in that subject. At these category meetings questions to be asked are reviewed and the appropriate answers are discussed. Individual associate examiners are responsible for the initial evaluation and are asked to assign a preliminary grade for each candidate. Unlike the previous system, the Board director may or may not be present during the examination of each candidate in each subject, thus providing the Board director with the ability to fulfill the role of a troubleshooter and to track the progress of all candidates as they proceed through the panel. At the end of each half-day examination session, the entire panel meets as a group. The performance of each candidate in each subject is then reviewed, and a consensus grade is determined for each subject. This process permits a longitudinal overview of a candidate's performance as well as the candidate's performance in each subject, thus providing a more comprehensive perspective of the candidate's knowledge.

Exit interviews with candidates and associate examiners, as well as an evaluation by professional psychometricians, have led the Board to believe that the examination of candidates by appointment within a panel system provides a marked increment in the efficiency and validity of the testing process. The American Board of Ophthalmology is dedicated to the continual improvement of its examination methods. Examination by appointment within a panel system marks a major phase in the evolution of the oral testing process.

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LETTERS TO THE JOURNAL

Clear Graft Two Years After Keratoplasty in Nephropathic Cystinosis

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Clinical Branch, National Eye Institute (M.I.K. and M.B.D.) and the Section on Human Biochemical Genetics, Human Genetics Branch, National Institute of Child Health and Human Development (W.A.G.), National Institutes of Health.

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Crystals typical of cystinosis that recurred within the corneal stroma of the donor button transplant in each eye of a patient with nephropathic cystinosis have been described.[1] These crystals, although subtle, were noted within six weeks of the transplant. The same patient in whom the recurrent crystals were reported was seen twice at the National Institutes of Health. The first examination occurred ten months after the corneal transplantation in the left eye and three months after the corneal transplantation in the right eye. In separate examinations, neither we nor R. Grutzmacher, M.D., who performed the surgery, observed any crystals in the donor buttons. One year later the right eye had become phthisical, but the corneal transplant of the left eye remained clear (Figure). No crystals were seen in the cornea, although abundant crystals were evident in the host cornea, iris, and on the surface of the lens.

These observations of clear donor cornea were confirmed in a second patient who maintained a clear graft,[2] and remains free of crystals two years postoperatively.

On the basis of our observations of these two cases, there does not appear to be convincing evidence that cystine crystals recur in donor corneal buttons for at least two years after transplantation. Such patients will be observed to determine whether this situation will change with time.

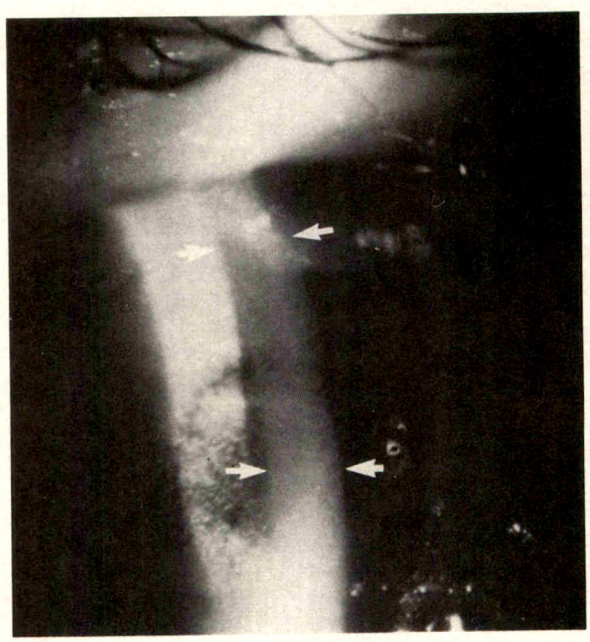


Figure (Kaiser-Kupfer, Datiles, and Gahl). Slit-lamp biomicroscopic photograph of left cornea. Slit beam in focus on clear cornea devoid of crystals (arrows), two years after corneal transplantation.

THE JOURNAL welcomes letters that describe unusual clinical or pathologic findings, experimental results, and new instruments or techniques. The title and the names of all authors appear in the Table of Contents and are retrievable through the Index Medicus and other standard indexing services. Letters must not duplicate data previously published or submitted for publication. Each letter must be accompanied by a signed disclosure statement and copyright transfer agreement published in each issue of THE JOURNAL.

Letters must be typewritten, double-spaced, on 8 1/2 x 11-inch bond paper with 1 1/2-inch margins on all four sides. (See Instructions to Authors.) They should not exceed 500 words of text. A maximum of two black-and-white figures may be used; they should be cropped to a width of 3 inches (one column). Color figures cannot be used. References should be limited to five.

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These instructions markedly limit the opportunity for an extended discussion or review. Therefore, THE JOURNAL does not publish correspondence concerning previously published letters.

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Leukemic Corneal Infiltrates

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Although leukemia can infiltrate virtually any tissue, it usually does not involve the avascular cornea. In their large series of patients with leukemia, Allen and Straatsma[1] showed that there was no corneal involvement beyond limbal infiltration. An extensive review by Kincaid and Green[2] found cases of ring ulcers in acute myeloblastic leukemia, although

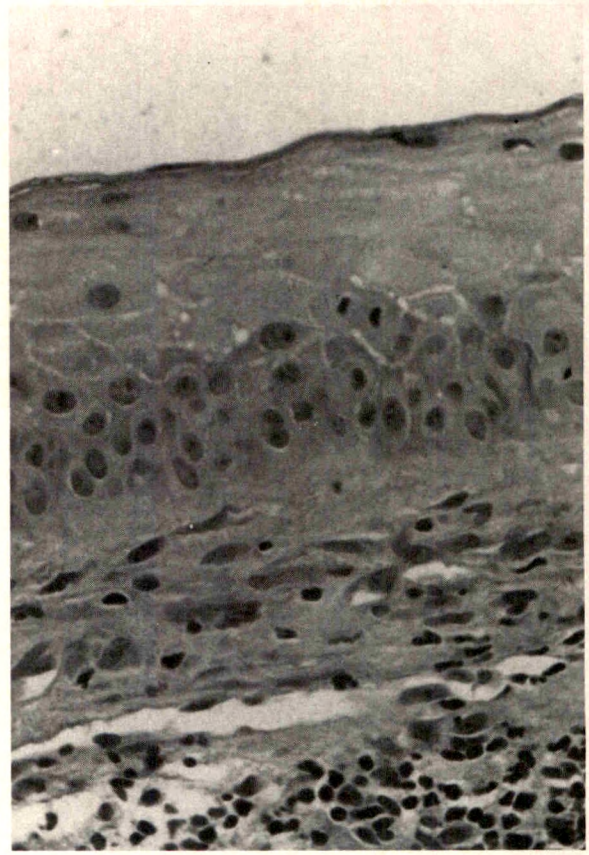


Fig. 1 (Eiferman, Levartovsky, and Schulz). Cornea with intact epithelium and heavy lymphocytic infiltration of the anterior stroma, involving Bowman's layer (hematoxylin and eosin, ×440).

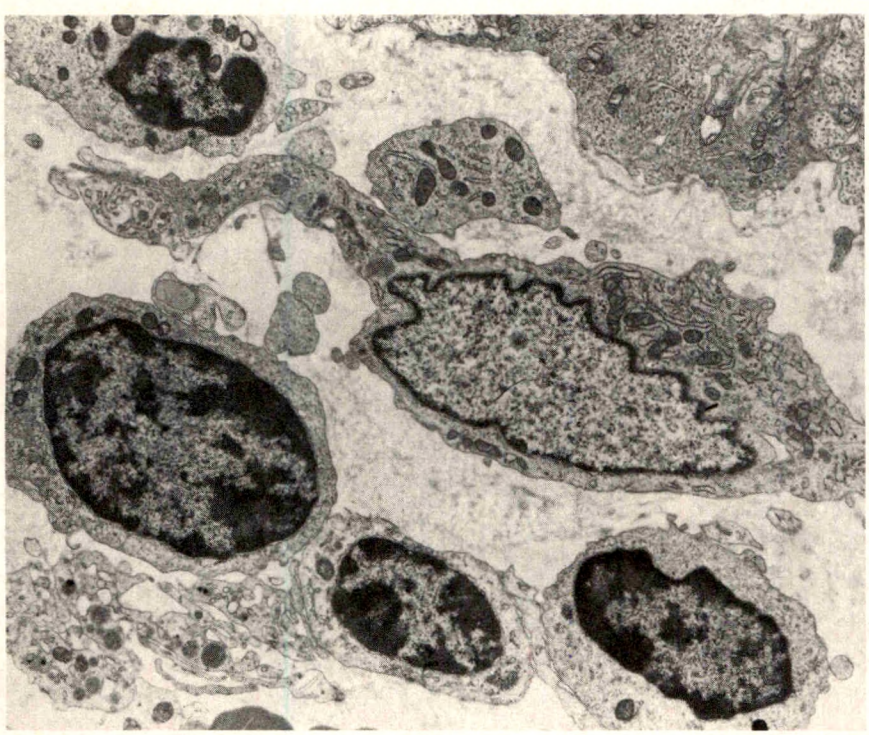


Fig. 2 (Eiferman, Levartovsky, and Schulz). Well-differentiated lymphocytes in anterior stroma (×11,000).

no cases of nonperipheral anterior stromal infiltrates were reported. We encountered a case of leukemic infiltrates in a clear corneal transplant in a patient with chronic lymphocytic leukemia.

An 83-year-old woman complained of a decrease in visual acuity. Her medical history included long-standing chronic lymphocytic leukemia, which required no treatment, and a corneal transplant eight years earlier for aphakic bullous keratopathy. On examination, numerous light gray circular infiltrates measuring 5 to 6 mm were noted in her transplanted eye, just below an intact epithelium. Results of cultures and scrapings did not show any growth. A tentative diagnosis of corneal graft rejection was made and topical and subconjunctival corticosteroids were applied without resolution of the infiltrates. On physical examination, the patient was found to have an enlarged liver and spleen, as well as numerous lymphocytes in her bone marrow. A corneal biopsy of the infiltrates was performed. Light and electron microscopy disclosed sheets of mature lymphocytes invading the superficial corneal stroma (Figs. 1 and 2).

Ophthalmologists should be aware of this ocular manifestation of chronic lymphocytic leukemia and realize that it may be the initial sign of an acute exacerbation.

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Pseudophakic Pigmentary Glaucoma

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Increased intraocular pressure associated with pigment dispersion has been reported after intraocular lens implantation.[1-3] We encountered two cases of pseudophakic pigmentary glaucoma after lens implantation.

A 72-year-old man underwent uncomplicated extracapsular cataract extraction in his left eye. An Anis nonangulated posterior chamber intraocular lens was placed within the capsule. Preoperatively, his intraocular pressure was within normal limits and his cup-to-disk ratios were normal and symmetric. The postoperative course was uneventful, with visual acuity of 20/20 in the left eye and normal intraocular pressures in both eyes.

Ten months postoperatively, visual acuity was 20/30 in the left eye, the intraocular pressure had increased to 50 mm Hg, and there was a left afferent pupillary defect. The anterior chamber was deep, with circulating pigment in the aqueous humor. The intraocular lens was in good position, but there was moderate iridodonesis, pigment dusting of the iris, and iris transillumination defects following the outer curves of both lens haptics. A Krukenberg spindle was observed in the left eye. Results of gonioscopy in the right eye were normal. Results of examination of the left anterior chamber angle showed a dramatic, diffuse increase in pigmentation. No angle structures were visible inferiorly because of the dense black pigment. The horizontal cup-to-disk ratios were R.E.: 0.5 and L.E.: 0.9. Results of perimetry were normal in the right eye, but showed marked, diffuse glaucomatous visual field loss in the left eye. Medical therapy was insufficient to control the patient's intraocular pressure, and he required filtering surgery.

A 67-year-old man underwent an uncomplicated extracapsular cataract extraction in the left eye. A medallion iris clip intraocular lens was secured to the iris with a 10-0 Prolene fixation suture. Postoperatively, intraocular pressure in the right eye was normal. Intraocular pressure in the left eye, however, increased to 32 mm Hg, despite treatment with timolol maleate 0.5%, dipivefrin hydrochloride 0.1%, and 50 mg of methazolamide twice daily. Iris transillumination defects developed in the intraocular lens haptics of the left eye. Gonioscopy disclosed normal pigmentation in the right angle, but a marked increase in pigmentation in the left angle. The horizontal cup-to-disk ratio remained 0.7 in the right eye but had increased to 0.9 in the left eye. A left afferent pupillary defect had developed. Results of perimetry were normal in the right eye but showed mild glaucomatous changes in the left eye. Pilocarpine was added to the patient's medical thera-

py, and his intraocular pressure has been controlled for the past year.

Previous reports of pseudophakic pigment dispersion have shown that the increased pressure is usually mild, can generally be controlled medically, and improves with the passage of time.[1,2] Although these observations may be true in most cases, pigment dispersion after lens implantation may also be associated with increases in pressure that can cause glaucomatous damage to the disk and visual field.

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Intraocular Dapiprazole to Reverse Mydriasis During Extracapsular Cataract Extraction

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Dapiprazole is a new alpha-1-lytic agent that is useful in reversing mydriasis by relaxing the dilator iris muscle.[1-3] Unlike cholinergic drugs it does not cause ciliary muscle spasm nor does it favor breakdown of the blood-aqueous barrier and eye congestion. Because it does not affect the constrictor muscle, it does not facilitate pupillary block as suggested by Iuglio[4] and Mapstone.[5] Unlike thymoxamine, dapiprazole can be prepared as a stable solution.

We tested the miotic efficacy of a buffered 0.1% dapiprazole solution administered intracamerally during extracapsular cataract extraction with posterior chamber lens implantation in otherwise healthy human eyes. In 40 consecutive patients the pupils were dilated preoperatively using 10% phenylephrine, 0.5% tropicamide, and 0.1% cyclopentolate. A 1:500,000 solution of phenylephrine was used in the infusion fluid to maintain dilation during cortex aspiration. Immediately after lens implantation and viscoelastic substance aspiration, each eye randomly received either 0.2 ml of 0.1% dapiprazole or 0.2 ml of balanced salt solution. These solutions were injected over the iris surface with a circular motion.

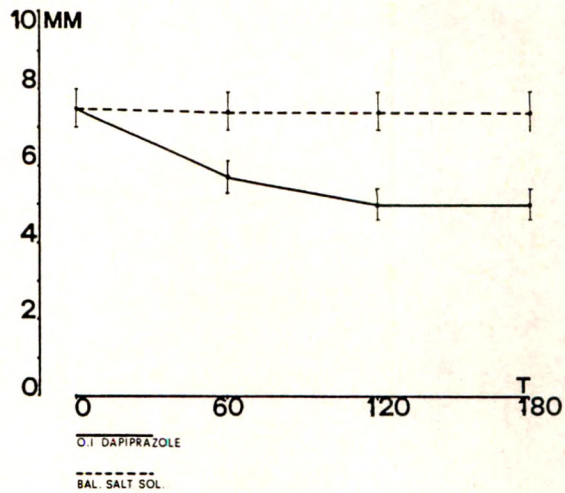


Figure (Prosdocimo and De Marco). Effect of 0.1% dapiprazole vs balanced salt solution on mydriasis. The dapiprazole reduced mydriasis by a mean of 30%, whereas the balanced salt solution had virtually no effect.

Each group contained 20 eyes and the pupillary diameter was measured with calipers immediately before and one, two, and three minutes after injection. Although there was virtually no change after injection of the balanced salt solution, the 0.1% dapiprazole solution reversed mydriasis, independent of iris pigmentation (Figure). On routine follow-up examination, neither toxic reactions nor significant differences in endothelial damage, intraocular pressure, or inflammatory response were observed between the two series.

We suggest the use of intraocular dapiprazole as a safe way to reverse sympathomimetically induced mydriasis during extracapsular cataract extraction. It may also be useful for other procedures, such as the combined cataract-keratoplasty intervention, which requires prompt miosis during surgery.

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Canalicular Laceration at Birth

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A wide variety of birth injuries to the globe and adnexa have been reported, including marginal eyelid laceration.[1,2] I report a case of disruption of the lacrimal canaliculus as a complication of delivery.

A 4,400-g boy was born to a 24-year-old primigravida woman after an uncomplicated pregnancy. The vaginal delivery included a right medial episiotomy and the use of low forceps. Immediately after birth, the delivery team noted forceps marks behind the left ear and lacerations of the right eyelids of the infant.

Results of examination under general anesthesia disclosed temporal chemosis and subconjunctival hemorrhage, but no laceration of the bulbar conjunctiva. The cornea was intact, the anterior chamber was formed, and intraocular pressure was normal. Neither intraretinal hemorrhages nor evidence of globe rupture were observed. There were multiple lacerations of the right upper eyelid, including a full-thickness vertical wound lateral to the punctum. A full-thickness laceration through the lower eyelid transected the canaliculus (Fig. 1).

Microsurgical repair of the lacrimal system and eyelids was performed, using the intubation set designed by Crawford.[3] The nasal ends of the silicone tube were passed through a silicone button, in a manner previously described.[4] The wound separation was relieved with 7-0 polyglactin 910 suture, which was passed through the tarsus and medial canthal tendon fibers. The pericanalicular connective tissue was apposed with 8-0 polyglactin 910 suture. The skin was closed with 9-0 nylon.

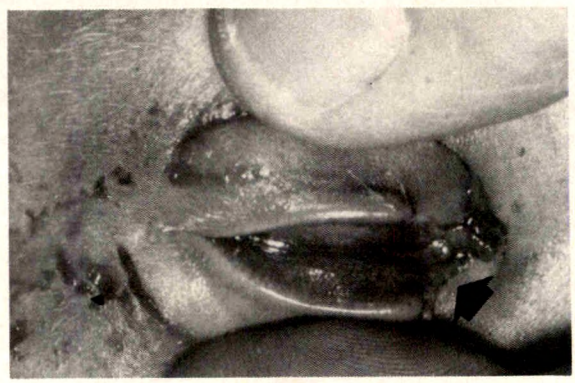


Fig. 1 (Harris). Multiple eyelid wounds sustained at birth include a laceration through the inferior canaliculus (arrow).

Five weeks after surgical repair, the silicone stent was removed because erosion through the puncta was noted. In 14 months of follow-up, there has been no epiphora and the system has been patent to Jones and Wobig's[5] primary dye testing and irrigation system. There are no signs of amblyopia or residual deformity (Fig. 2).

The exact mechanism of eyelid and canalicular injury in this case is unclear. Possible offenders include the delivery forceps, fingertips, and the episiotomy scissors.

The use of silicone tubes has become standard practice in the repair of canalicular lacerations. Although the caliber of currently available tubing may have contributed to erosion of the neonatal puncta, tear drainage in this patient has remained normal.

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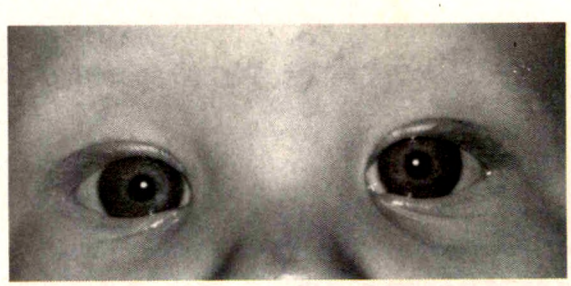


Fig. 2 (Harris). Eight months after repair, without epiphora or deformity.

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A Modification in the Frontalis Suspension Procedure

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Frontalis suspension is the surgical procedure of choice to correct blepharoptosis with absent or poor levator muscle function.[1] This operation can be performed with either nonabsorbable suture material or fascia lata. When using fascia lata, we have encountered difficulty applying sufficient countertraction to the eyelid margin as the fascia lata is passed subcutaneously from the eyelid to the eyebrow incisions. Forceps with teeth, if large enough to stabilize the eyelid properly, occasionally lead to unwanted eyelid marginal trauma.



Fig. 1 (Duker and Nelson). Towel clip.



Fig. 2 (Duker and Nelson). Two towel clips shown straddling the middle eyelid incision in the proper position to apply countertraction. Note the Wright needle with fascia lata in place, ready for subcutaneous passage.

To eliminate this difficulty and to prevent trauma, we use a modified version of Crawford's original frontalis suspension technique for the placement of the incisions and the passage of the fascia lata.[2] With the fascia lata on a Wright needle, before its subcutaneous passage from the eyelid to the eyebrow, we grasp the eyelid margin on each side of the incision with a plastic towel clip (Fig. 1). The surgical assistant then holds the towel clips and provides inferiorly directed countertraction as the fascia lata is passed superiorly to the proper

eyebrow incision (Fig. 2). The towel clips are removed after this step is completed. Any alteration in the skin of the eyelid margin from the grip of the towel clip disappears within minutes.

This technique has been used in over 100 frontalis suspension operations with no occurrences of eyelid deformation. The plastic towel clips are inexpensive and can be resterilized for repeated use. We have found this modification to be the simplest, most reliable, and most nontraumatic way in which to apply countertraction during the frontalis muscle suspension procedure.

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Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Incidence of Subcortical Lesions Not Increased in Nonarteritic Ischemic Optic Neuropathy on Magnetic Resonance Imaging

EDITOR:

In the article "Incidence of subcortical lesions not increased in nonarteritic ischemic optic neuropathy on magnetic resonance imaging" (Am. J. Ophthalmol. 104:398, October 1987), by W. M. Jay and M. R. Williamson, the authors state: "Patients with nonarteritic ischemic optic neuropathy do not appear to have an increased incidence of generalized cerebral vascular disease." However, as only nine patients with ischemic optic neuropathy and a control group of 11 patients were studied, the result of any statistical test to determine a significant difference between groups will be low. Therefore, conclusions stating no difference between groups must be viewed with extreme caution.

A test more appropriate than the *t*-test for their series is the Mann-Whitney U Test R,[1] which makes no assumptions about the data being from normal distributions. Applied to the authors' data, this test also shows no difference between groups ($P = .29$). However, if they had a sample size of 40 patients per group (approximately four times the size of the present study) and the same sample distribution of the number of lesions as reported in the authors' article, these two groups would be statistically different ($P < .05$) and patients with nonarteritic ischemic optic neuropathy would have an increased incidence of cerebrovascular disease.

In our series of 212 patients with ischemic optic neuropathy,[2] we found that patients with idiopathic ischemic optic neuropathy or nonarteritic ischemic optic neuropathy and systemic hypertension were at a statistically significant increased risk of developing cerebrovascular and cardiovascular disease when compared to age-, sex-, and race-matched control groups. We found that this association may have been the result of the large sample size ($N = 212$) of our series. Previous reports perhaps failed to find such a relation because of their smaller sample size (only 83 patients in the previously largest series[3]). This difference in conclusions, which is perhaps based on the difference in sample size, stresses the importance of adequate sample sizes in clinical studies.

When a statistically significant association is present, a positive relationship can be confidently stated. However, one must be extremely cautious before suggesting a negative relationship or a lack of association, especially in studies with limited sample size, such as the one reported by the authors.

We commend these authors for using magnetic resonance imaging to study the relationship between nonarteritic ischemic optic neuropathy and cerebrovascular disease. We hope that a further study with an adequate sample

size will be undertaken. Based on our calculations, such a study might indeed confirm our findings of the risk of cerebrovascular disease in such patients.

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STUART L. FINE, M.D.
Baltimore, Maryland

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Reply

EDITOR:

We thank Dr. Guyer and associates for their comments. Our article illustrates the usefulness of magnetic resonance imaging in studying the relationship between neuro-ophthalmologic conditions and generalized cerebrovascular disease. We agree that a larger series of patients should be compiled and hope our article will stimulate other investigators to pursue this line of research.

WALTER M. JAY, M.D.
MICHAEL R. WILLIAMSON, M.D.
Little Rock, Arkansas

Can the Risk of Acetazolamide-Induced Aplastic Anemia be Decreased by Periodic Monitoring of Blood Cell Counts?

EDITOR:

This brief note is to congratulate you on the superb editorial "Can the risk of acetazolamide-induced aplastic anemia be decreased by periodic monitoring of blood cell counts?" by A. Zimran and E. Beutler (Am. J. Ophthalmol. 104:654, December 1987). The authors have realistically examined most of the complexities relating to the use of acetazolamide, a potentially life-threatening medication, and the management of a potentially blinding disease. Some of the recent publications have oversimplified this issue. Prudent, knowledgeable, and caring physicians will give different advice to different patients.

The editorial does not provide definite advice regarding the proper management of cases in which the use of acetazolamide is considered appropriate. Its failure to support a specific position is the strongest and the most appropriate comment that could be made.

In publishing this editorial you have performed an important service for physicians and patients alike.

GEORGE L. SPAETH, M.D.
Philadelphia, Pennsylvania

Clinical Alert: Pharmafair 15-ml BSS Solution

Flaking of lettering on 15-ml containers of Pharmafair BSS solution has raised the possibility of particles contaminating the fluid or surgical field during surgery. The lot numbers affected are 4876 (expiration date, 4/89) and 5072 (expiration date, 6/89). The company has voluntarily recalled these two lots. It is recommended to discontinue use of products with these two lot numbers and routinely inspect plastic 15-ml containers of BSS before use for evidence of flaking. This alert is in addition to the previous clinical alert highlighting the problem of corneal clouding encountered with Pharmafair BSS lot numbers 4000, 4945, 4017, 4207, and 3797.

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Atlas of Pediatric Ophthalmology. By Joseph H. Calhoun, Leonard B. Nelson, and Robison D. Harley. Philadelphia, W. B. Saunders Company, 1987. 320 pages, index, illustrated. $65

Reviewed by ARTHUR L. ROSENBAUM
Los Angeles, California

The primary goal of the authors has been to design a surgical atlas for instructing residents and fellows in the most common surgical procedures encountered during a pediatric ophthalmology rotation. Two thirds of the book is devoted to a description of strabismus surgical techniques. The last 100 pages detail nasolacrimal, blepharoptosis, and congenital cataract and glaucoma surgery. Thus, the student has all the common surgical descriptions available in one volume.

The most exciting aspect of the book is the 22-page narrative in the first chapter on the indications for strabismus surgery. This text is a lucid and reasoned methodology concerning the details of strabismus surgical decision making. It has a logical structure upon which the physician can base decisions to proceed with the surgical techniques that then follow.

There is an excellent description of limbal and cul-de-sac conjunctival incision techniques and several well-illustrated rectus muscle recession and resection procedures. The book contains a detailed description of superior oblique surgical operations, including plication and Harada-Ito techniques for torsional correction. There is a current description of adjustable suture procedures, although no credit is given to Dr. Arthur Jampolsky, who created this technique. The posterior fixation, "faden," and Jensen procedures are detailed. However, no other transposition procedures, such as total muscle transposition for double elevator palsy or seventh nerve palsy, are described. There is no mention of botulinum toxin injection as a treatment for strabismus alone or in conjunction with surgery and there is no section on surgical complications.

The drawings are black-and-white. There are no color plates or clinical surgical photographs for comparison to the drawings, which would be helpful for beginning surgeons to appreciate tissue planes in color.

The book contains an excellent description of infantile nasolacrimal procedures, including probing, silicone tube intubation, and dacryocystorhinostomy. The chapter on blepharoptosis contains standard procedures that have been reported in other surgical texts. The congenital cataract and glaucoma surgery drawings are not detailed enough to allow the surgeon to understand clearly the limbal anatomy or the important angle structures. Color photographs of actual clinical cases or more detailed color drawings, including gonioscopically magnified views, are necessary. There is no mention of trabeculectomy, a commonly performed procedure for congenital glaucoma.

The book's great advantage is that most commonly performed pediatric ophthalmology surgical procedures can be found in one volume. The procedures are accurate and the descriptions of these techniques are clearly written. As the authors mention, most of the strabismus surgical procedures have been described in detail in the Atlas of Strabismus Surgery, by Marshall Parks, published in 1983.

If one does not own a strabismus or blepharoptosis surgical atlas, this volume permits easy access to the entire range of pediatric ophthalmology surgical procedures.

Manual of Clinical Problems in Ophthalmology. By John W. Gittinger, Jr., and George K. Asdourian. Boston, Little, Brown and Company, 1987. Softcover, spiralbound, 218 pages, index. $19.50

Reviewed by H. STANLEY THOMPSON
Iowa City, Iowa

This is the latest in a large series of medical spiralbound manuals produced by Little, Brown and Co. It is indeed a manual, the kind of book that an ophthalmology resident would like to have at hand while seeing patients. Various topics in medical ophthalmology and neuro-ophthalmology are covered in 66 brief reviews. The type is small, but crisp and clear.

The reviews are well organized and directed toward understanding the disease process and recognition of the chief diagnostic features. Each essay closes with a paragraph or two on modern management.

I find the references particularly appealing: a short note is appended to each one, giving the reader a taste of what to expect in the review. There are ten to 20 recent references with each review, which is just enough to get the student started on the way to a deeper understanding of the subject.

A spiral binding may look untidy but it allows the book to be folded back on itself or opened flat at any page. To have a manual bound this way somehow suggests that it might be used as a reference work while the reader has both hands at work on the patient. Thus, I am inclined to forgive the binding.

Books Received

Highlights in Neuro-ophthalmology. Edited by S. Ishikawa, K. Mukuno, S. Uga, and J. T. W. Van Delen. Amsterdam, Aeolus Press, 1987. 265 pages, index, illustrated. $80

Thirty-five of the papers given at the International Neuro-ophthalmology Society meeting in Hakone, Japan, in June 1986 have been published in this volume. Topics include optic nerve fibers, optic neuropathy, the optic nerve head, optic nerve tumors, the retinal nerve fiber layer, evoked potentials, ocular movement abnormalities, case reports, and new therapies and examination techniques.

Meetings

OCULAR MICROBIOLOGY AND IMMUNOLOGY GROUP: 22nd ANNUAL MEETING

The 22nd annual meeting of the Ocular Microbiology and Immunology Group was held Nov. 7, 1987, at the Hyatt Regency Hotel in Dallas, Texas.

Several papers dealt with the diagnosis and treatment of endophthalmitis. G. A. Stern, J. Silberger, and Z. S. Zam described the effect of repetitive intravitreal antibiotic injections in the treatment of experimental bacterial endophthalmitis. They found that five of 26 patients with endophthalmitis did not improve with a single intravitreal injection and they suggested that repetitive intravitreal injections may be necessary to reduce the concentration of organisms.

J. Baum, M. Barza, and M. Sliwkowski studied the ocular pharmacokinetics of LY146032, teicoplanin, and vancomycin in a rabbit mode of endophthalmitis. They believed it was necessary to determine the half-life of a drug in an inflammatory reaction in order to determine whether therapeutic levels are being achieved.

R. L. Manka and W. H. Stern described a case of *Staphylococcus aureus* endophthalmitis masquerading as chronic uveitis. This low-grade postoperative inflammation, probably caused by sequestered material, continued for several months before a diagnosis was made.

P. R. Pavan, C. E. Margo, and L. R. Groden described a case of granulomatous vitritis following treatment of endophthalmitis caused by a coryneform bacteria. The patient died 5½ weeks after surgery, and foamy histiocytes similar to those seen in Whipple's disease were found in the vitreous. *Corynebacterium* has been implicated in the pathogenesis of Whipple's disease.

R. C. Arffa and A. Eller described two cases of *Listeria monocytogenes* endophthalmitis. Both patients had acute iritis and hypopyon in previously normal eyes. One patient was in good health and the other had a porcine heart valve and a previous episode of bacterial sepsis. Both patients responded to systemic intravenous ampicillin but both also developed retinal detachments.

A. A. Bialasiewicz, G. Koniszewski, and R. Breitbach described a 79-year-old patient who developed a recurring iridocyclitis after cataract surgery. *Staphylococcus epidermidis* was eventually isolated from this so-called "toxic lens" syndrome. The bacteria may have been harbored in the lens capsule.

J. D. Shepard, R. A. Nozik, T. A. Friberg, S. B. Kalish, J. A. Goldsmith, and S. R. Zeiss described the role of the enzyme-linked immunosorbent assay test in the diagnosis of tuberculous uveitis. Anti-purified protein derivative antibodies in the aqueous humor may help establish a diagnosis of tuberculous uveitis in

purified protein derivative-positive patients with idiopathic uveitis.

J. D. Nelson described the activation of ocular toxoplasmosis after a subconjunctival corticosteroid injection in a patient who had cataract surgery. He urged caution in the administration of subconjunctival corticosteroid in patients with inactive chorioretinal scars.

Y. J. Gordon, T. Araullo-Cruz, and E. Romanowski described a new concept in herpetic latency. This new concept defines latency as a state in which at least one viral gene is transcribed, but full expression is blocked, and no live virus is produced.

S. M. Mahjoub, J. P. Ganley, R. Misra, and M. P. Langford studied the neurovirulence and retinal necrosis produced by herpes simplex virus type 2 in mice. One strain was less neurovirulent than the other but caused retinal necrosis in mice.

M. D. Trousdale and J. M. Delmage assessed epidermal growth factor and fibronectin in herpes simplex virus type 1 infection. Neither epidermal growth factor nor fibronectin altered the antiviral activity of antiviral medications nor did they enhance ocular herpetic infections.

J. Schulman, G. Peyman, T. Albrecht, C. H. Lee, and L. Steahly described the effect of two calcium channel blockers on cytomegalovirus. Papaverine was a more potent inhibitor of cytomegalovirus replication than verapamil. Both agents may be potentially beneficial in the treatment of cytomegalovirus retinitis possibly through the cyclic-GMP system.

M. P. Langford, R. M. Kadi, J. P. Ganley, and M. Yin-Murphy described the inhibitory activity of recombinant interferon α and β against acute hemorrhagic conjunctivitis virus. They suggest that some recombinant interferons may be equally or more effective than natural interferon in preventing or inhibiting the spread of acute hemorrhagic conjunctivitis during epidemics.

P. A. Rapoza, S. K. West, S. Katala, S. L. Johnson, V. Turner, and H. R. Taylor described direct immunofluorescence monoclonal antibody staining of conjunctival smears for trachoma. This relatively inexpensive test is easy to perform and applicable to large-scale field studies.

I. Sandstrom, I. Kallings, and B. Helen reported a long-term follow-up of 160 infants with neonatal conjunctivitis. All cases of chlamydial conjunctivitis were cured with oral erythromycin. IgM antibodies to *Chlamydia* were thought to be of diagnostic value.

S. I. Butrus, A. M. A. Irani, K. F. Tabbara, and L. B. Schwartz described an increased number of T mast cells in vernal conjunctivitis. T mast cells were tryptase-positive and kinase-negative while TC mast cells were tryptase-positive and kinase-positive. An increased number of TC mast cells was found in giant papillary conjunctivitis.

N. R. Barney, R. M. Briggs, K. J. Bloch, and M. R. Allansmith presented evidence that conjunctival mast cells are of the connective tissue type. Their findings were based on mast cell degranulation response to a single application of compound 48/80 and decreased mast cell numbers in response to multiple applications of 48/80.

A. Y. Matoba and M. Pollack evaluated the effect of retinoic acid and retinol on interferon gamma induced class II antigen expression on corneal and dermal fibroblasts. They found that retinoic acid enhances expression of class II antigens and they suggest that it could enhance rejection in patients who have had corneal transplants.

G. Grabner, I. Klantschnig, J. Beczak, and I. Baumgartner described the production of a thymocyte-inhibiting cytokine by the human retinoblastoma cell line Y-79. Possible biological significance of this interleukin I inhibiting cytokine remains to be elucidated.

C. M. Kalsow and L. A. Donoso described the response of guinea pigs to peptide M of retinal S antigen. Peptide M, which induces experimental allergic uveitis in Lewis rats, showed immunofluorescence reactivity with Müller cells in the guinea pig retina. These results were consistent with previous observations of Müller cells and experimental uveitis.

R. M. Rubin, L. Elzinga, W. M. Bennett, and J. T. Rosenbaum studied the effects of fish oil dietary supplementation on endotoxin-induced uveitis. They suggest that fish oil intake, by altering arachidonic acid metabolite production, may reduce vascular permeability modestly without affecting the cellular infiltration associated with anterior uveal inflammation.

K. J. Johns, D. M. O'Day, C. M. Parrish, and J. H. Elliott discussed corneal melting after intraocular lens implantation in patients with collagen-vascular diseases. This condition may be caused by the lens implant, dry eye, or production of lytic enzymes. The visual outcome is usually poor.

P. B. Donzis, B. J. Mondino, and B. A. Weissman described microbial contamination of contact lens care systems with *Acanthamoeba*. All seven patients with *Acanthamoeba* keratitis had *Acanthamoeba* isolated from their care systems. This infection is usually associated with the use of homemade saline solutions.

M. B. Moore, R. Silvany, J. P. McCulley, and R. W. Bowman evaluated the susceptibility of *Acanthamoeba* to current contact lens disinfecting systems. They recommended heat disinfection of lenses or hydrogen peroxide for at least four hours.

M. S. Osato, N. M. Robinson, K. R. Wilhelmus, and D. B. Jones pointed out that *Acanthamoeba* produced "trails" on culture plates. These trails can be differentiated from trails produced by other organisms based on morphology and preservation upon serial transfer to fresh medium.

J. B. Robin, R. Chan, and J. Salazar evaluated fluorescein-conjugated lectins in the visualization and possible identification of *Acanthamoeba*. These ubiquitous proteins bind specifically with carbohydrate moieties and can be used to differentiate *Acanthamoeba* from other organisms.

G. O. D. Rosenwasser, D. Miller, C. F. Gottlieb, and E. Alfonso studied the cytopathologic effects of cobalt 60 radiation on cysts of *Acanthamoeba polyphaga*. They showed an inverse relationship of total radiation dose with cobalt 60 to cytopathologic effects, with effects becoming noticeable with doses as low as 5,000 rad.

R. A. Eiferman and R. E. Nordquist described the successful treatment of *Acanthamoeba* keratitis by debridement of a superficial corneal infiltrate. They suggest that early infection with *Acanthamoeba* may only involve the epithelium and that it may be possible to remove the offending organism by debridement before it infects the underlying stroma.

J. H. Brinser, L. R. Groden, and A. Weiss identified 811 isolates of streptococci from 369 patients over a nine-year period. Of these 61.5% were alpha streptococci and 30% were pneumococci. When these organisms were susceptible to aminoglycosides, gentamicin was more likely to be effective than tobramycin.

J. K. G. Dart, J. Peacock, I. Grierson, and D. Seal described contact lens, corneal, and bacterial interactions in a rabbit model. They found that the continuous wear of a Hydrogel contact lens did not increase adherence of *Pseudomonas aeruginosa* to the rabbit cornea; however, the lens surface could be colonized for up to one week without causing ocular inflammation.

A. Selwa, F. Al-Hazzaa, and K. F. Tabbara described their experience in Saudi Arabia with bacterial keratitis after penetrating keratoplasty. In corneal transplant patients 12% developed bacterial keratitis, and these investigators believe this high incidence could be minimized or avoided by appropriate selection and better preoperative and postoperative management of trichiasis. Other conditions that predispose to infection included eroding sutures, dry eye syndrome, lagophthalmos, nasolacrimal duct obstruction, blepharitis, vitamin A deficiency, and adverse climatic conditions.

H. S. Geggel and T. E. Gillette described a patient who developed an apparently sterile keratitis 3½ years after radial keratotomy. The cause of the corneal infiltrate was unclear.

R. Weisenthal, J. H. Krachmer, R. Folberg, W. E. Whitson, and S. P. Dunn described crystalline keratopathy after corneal transplantation in three patients. This condition mimics the crystalline keratopathy produced by *Streptococcus viridans*. In one patient, the crystals were caused by calcium.

M. B. Hamill described crystalline keratopathy after corneal transplantation for *Acanthamoeba* keratitis. In these patients, *Streptococcus* organisms were isolated. The infections may have been associated with the excessive use of topical corticosteroids.

L. D. Ormerod, L. P. Fong, and C. S. Foster described microbial keratitis in 51 patients with mucosal scarring disorders and Sjögren's syndrome. Most cases were caused by gram-positive organisms. Factors such as trichiasis, topical corticosteroids, and bandage contact lenses increased the risk of infection.

R. P. Kowalski, M. I. Roat, J. C. Stuart, and M. O. Ritter described the treatment of fungal keratitis with intracorneal stromal injections of antifungal agents. These rabbit studies showed good efficacy without significant toxic effects.

D. S. Rootman and J. M. Hill described iontophoresis with tobramycin in the treatment of experimental *Pseudomonas* keratitis. Iontophoresis was significantly better than topical fortified antibiotic eyedrops in reducing viable bacteria and it may be a useful adjunct in the treatment of severe corneal bacterial infections.

T. O'Brien, M. R. Sawusch, J. Valentine, and J. D. Gottsch described topical ciprofloxacin therapy for aminoglycoside-resistant *Pseudomonas* keratitis. This quinolone antibiotic is highly

active against *Pseudomonas* and the investigators believe that ciprofloxacin may be clinically useful in the treatment of aminoglycoside-resistant *Pseudomonas* keratitis.

M. R. Sawusch, T. P. O'Brien, and J. D. Gottsch evaluated topical imipenem, a highly potent β-lactam antibiotic, in the treatment of aminoglycoside-resistant *Pseudomonas* keratitis. This drug has the broadest spectrum of any antibiotic and may be useful in the treatment of *Pseudomonas* keratitis.

K. K. York and N. Burstein evaluated the ocular toxicity of polyvinylpyrrolidine-iodine, a broad-spectrum antimicrobial used as an ophthalmic prepping solution. Because of its broad spectrum and apparently low toxicity, this agent may be useful in the treatment of corneal and conjunctival infections.

J. D. Hofbauer, T. Pettit, and B. J. Mondino described corneal endothelial damage in a patient whose eyelids were prepared with Hibiclens before an upper eyelid blepharoplasty. Bullous keratopathy developed but eventually resolved, leaving a corneal haze.

M. Aswad, J. Baum, M. Barza, P. Weinstein, and J. Groden described bilateral keratitis in a patient with Lyme disease. This juvenile rheumatoid arthritis-like illness, first described in Lyme, Connecticut, is caused by *Borrelia burgdorferi*. The keratitis developed five years after the initial episode of arthritis and was described as a bilateral, patchy avascular process involving both superficial and deep stroma. Both corneas cleared completely after topical corticosteroid treatment. The investigators believed that the observed keratitis was more likely to be an immunologic reaction than a simple infection. These patients may have a positive FTA-Abs but a negative rapid plasma reagin.

J. E. Sutphin, J. A. Hazlehurst, D. E. Cink, and R. E. Reifschneider described a case of granulomatous scleritis caused by *Mycobacterium*. Acid-fast bacteria were identified in the granulomas and the patient was treated with antituberculous medications.

R. W. Enzenauer, F. M. Cornell, J. D. Brooke, and C. E. Butler described *Nocardia asteroides* keratitis in a soft contact lens wearer. Poor hygiene and a contaminated contact lens case were implicated in this infection. Trimethoprim-sulfamethoxazole given topically and orally were effective in treating the keratitis.

S. C. Pflugfelder, J. Kronish, D. Miller, S. Ullman, and E. Alfonso described two cases of necrotizing keratitis caused by *Capnocytophaga ochracea*. Predisposing factors included exposure to organic solvent and excessively applied topical anesthetics. Both eyes developed peripheral ring infiltrates followed by stromal necrosis and eventual perforation. Clindamycin is the drug of choice in the treatment of this gram-negative anaerobic bacillus.

S. P. Holland, S. Rosenfeld, and S. Ullman described a corneal ulcer caused by *Achromobacter xylosoxidans* in a patient who used contaminated timolol eyedrops. This gram-positive rod is a rare cause of corneal ulceration and may or may not respond to treatment with carbenicillin, the drug of choice.

MITCHELL FRIEDLAENDER

ABSTRACT DEPARTMENT

Edited by David Shoch, M.D.

Acta Ophthalmologica

Use of botulinum toxin in blepharospasm and other facial spasms. Ruusuvaara, P., and Setala, K. (Univ. Eye Clin., Univ. Helsinki, SF-00290 Helsinki 29, Finland). Acta Ophthalmol. 65:313, 1987.

Of 13 patients, nine had essential blepharospasm, one had Meige's syndrome, and two had hemifacial spasm. All responded well to botulinum toxin therapy, with control of the spasm varying from one to 38 weeks (mean, 11 weeks). In contrast to previous studies, dose of botlinum did not need to be increased to achieve relief a second and third time. The only serious complications were a severe bilateral blepharoptosis in one patient, which gradually resolved, and a seventh nerve palsy in one patient, which lasted three weeks. One patient with myokymia had complete relief of the twitching of her eyelid for nine months. (5 figures, 5 tables, 15 references)—David Shoch

Exfoliation syndrome in enucleated haemorrhagic and absolute glaucoma. Karjalainen, K., Tarkkanen, A., and Merenmies, L. (Univ. Eye Clin., 00290 Helsinki, Finland). Acta Ophthalmol. 65:320, 1987.

This retrospective study examined 172 eyes enucleated for hemorrhagic and absolute glaucoma. Thirty-three percent of the eyes with hemorrhagic glaucoma and 22% of the eyes with absolute glaucoma had evidence of the exfoliation syndrome. In patients over the age of 70 years, the incidence of both hemorrhagic and absolute glaucoma was about 50%. Although the study was performed only on enucleated eyes, it does confirm the widely held belief that exfoliative glaucoma is more difficult to control than open-angle glaucoma and that it can lead to neovascular glaucoma in older patients. (1 figure, 3 tables, 6 references)—David Shoch

Comparison of sodium hyaluronate and methylcellulose in extracapsular cataract extraction. Thomsen M., Simonsen, A. H., and Andreassen, T. T. (Dept. Ophthalmol., Centralsygehuse, DK-4700 Naestved, Denmark). Acta Ophthalmol. 65:400, 1987.

Thirty patients randomly received either 1% sodium hyaluronate or 2% methylcellulose during extracapsular cataract surgery with posterior chamber implantation. In both groups the material was aspirated at the end of the procedure. The authors found no difference in central corneal thickness, intraocular pressure, and aqueous flare in the first postoperative month. Mean intraocular pressure was lower than the preoperative pressure in both groups of patients. No ill effects from the use of methylcellulose were noted. (2 figures, 3 tables, 18 references)—David Shoch

British Medical Journal

Diagnosis of ophthalmia neonatorum. Winceslaus, J., Goh, B. T., Dunlop, E. M. C., Mantell, J., Woodland, R. M., Forsey, T., and Treharne, J. D. (Whitechapel Clin., The London Hospital, London, England E1 1BB). Br. Med. J. 295:1377, 1987.

In 86 eyes from babies with ophthalmia neonatorum, *Neissseria gonorrhoeae* was isolated from eight, *Chlamydia trachomatis* from 44, and other bacteria alone from 20. Fourteen eyes had negative bacteriologic cultures. However, three of the neonates with negative cultures had antichlamydial IgM antibodies. Thus, more than one half of the infants had chlamydial conjunctivitis. The simplest technique for making this diagnosis was a Gram-stained conjunctival smear. The smear correlated well with results of culture and assessment by the microimmunofluorescence test. This test is simple and inexpensive and is probably the most useful test in developing countries. (3 tables, 15 references)—David Shoch

Cancer

Progressive loss of vision in patients with high-grade non-Hodgkin's lymphoma. Holte, H., Saeter, G., Dahl, I. M., and Abrahamsen, A. F. (Lab. Immunology, Dept. Pathol., Inst. Cancer Res., Norwegian Radium Hosp., Montebello, N-0310 Oslo 3, Norway). Cancer 60:2521, 1987.

Three patients with non-Hodgkin's lymphoma responded well systemically to combined

treatment with cyclophosphamide, doxorubicin hydrochloride-prednisone, and methotrexate. However, all three patients developed bilateral optic neuritis. Although the optic neuritis may have been caused by the drugs used to treat the lymphoma, in one case lymphocytic infiltration of the optic nerves was demonstrated by x-ray studies and in all three there was a response of the neuritis to increased corticosteroids and to local radiation. When progressive loss of vision occurs in patients with high-grade lymphomas, lymphomatous involvement of the optic nerve is the most probable cause. The loss of visual acuity may be the only sign of recurrent lymphoma. (1 table, 18 references)—David Shoch

Eye

Botulinum toxin A induced protective ptosis. Adams, G. C. W., Kirkness, C. M., and Lee, J. P. (Dept. Clin. Ophthalmol., Inst. Ophthalmol., Moorfields Eye Hosp., City Road, London, England EC1 2PD). Eye 1:603, 1987.

Botulinum toxin was injected into the levator muscle producing a blepharoptosis of the upper eyelid in 15 patients with indolent ulcers of the cornea. The average time for development of complete blepharoptosis was three days. Subsequent injection was necessary in four of the patients. The blepharoptosis persisted from one to five weeks before recovery began. The mean recovery period was eight weeks. In one patient the blepharoptosis lasted seven months. Twelve of the 15 patients had complete corneal healing as a result of protection by the eyelid. Weakness of the superior rectus muscle occurred in 12 patients and lasted about six weeks. (3 figures, 1 table, 7 references)—David Shoch

Graefe's Archive for Clinical and Experimental Ophthalmology

Function of the diabetic retina after panretinal argon laser coagulation. Seiberth, V., Alexandridis, E., and Feng, W. (Dept. Clin. and Experimental Ophthalmol., University Eye Clin., Im Neuenheimer Feld 400, D-6900 Heidelberg, West Germany). Graefes Arch. Clin. Exp. Ophthalmol. 225:385, 1987.

In 16 patients with diabetes, one eye received 400 large laser spots of panretinal argon laser photocoagulation and the fellow eye received 1,500 small spots. The total coagulated area was approximately equal in the two eyes. Although there was a marked loss of retinal function immediately after coagulation, much of it returned. There was no statistical difference between the eyes treated with large spots and those treated with small spots. Visual acuity was lost in 8% of the eyes. Six months after coagulation, visual field measurements were about the same as the preoperative values in 50% of the eyes; in approximately 45% of the eyes, there was clear deterioration of the fields. Persistent field defects appeared to occur less frequently in eyes that had small coagulation spots, but this tendency was not statistically significant. (3 figures, 4 tables, 18 references)—David Shoch

5-Fluorouracil for trabeculectomy in glaucoma. Kitazawa, Y., Taniguchi, T., Nakano, Y., Shirato, S., and Yamamoto, T. (Dept. Ophthalmol., Gifu Univ. School of Med., 40 Tsukasa-machi, Gifu-shi 500, Japan). Graefes Arch. Clin. Exp. Ophthalmol. 225:403, 1987.

The 22 patients in this study all had had at least two failed trabeculectomies before undergoing another standard trabeculectomy. Of the 22 eyes, 20 received 5 mg of 5-fluorouracil once a day throughout the first postoperative week and once every other day during the second postoperative week. Life tables were used to analyze the results. The control group consisted of 24 patients who had undergone trabeculectomy after a previous failure but did not receive 5-fluorouracil. After 18 months the probability of success was 68% in the treated eyes and 10% in the untreated eyes, the difference being highly significant statistically. Postoperative treatment with subconjunctival 5-fluorouracil does seem to improve the prognosis after trabeculectomy in patients with previous failures. (3 figures, 4 tables, 7 references)—David Shoch

A comparative study between the PAM and the laser interferometer in cataracts. Dantiles, M. B., Edwards, P. A., Kaiser-Kupfer, M. I., McCain, L., and Podgor, M. (Clin. Branch, National Eye Inst., NIH, 9000 Rockville Pike, Bldg. 10, Room 10N226, Bethesda, MD 20892). Graefes Arch. Clin. Exp. Ophthalmol. 225:457, 1987.

The Guyton-Minkowski potential acuity meter and the laser interferometer were used to determine potential visual acuity in 35 cataractous eyes when the cataracts were not too dense and there was good visualization of the optic nerve head. Both instruments were found to be reliable in distinguishing between visual loss caused by cataracts and that caused by retinal changes, with accuracies of 94% for the Guyton-Minkowski machine and 88% for the laser interferometer. However, in eyes with advanced cataracts in which the optic disk was barely visible, both instruments were unreliable (accuracies of 33% and 53%, respectively). The most accurate information was observed in severely myopic eyes with axial lengths greater than 29 mm, moderate cataracts, and poor visual acuity. In these eyes, both instruments were reliable in separating visual loss caused by cataracts from visual loss caused by retinal changes. (6 tables, 11 references)—David Shoch

Journal of Medical Genetics

Prevalence and mode of inheritance of major genetic eye diseases in China. Hu, D. N. (Rm. 402, 490 Shan Xi Nan Road, Shanghai, China). J. Med. Genet. 24:584, 1987.

Genetic information on ocular disease was collected for 700,000 people in China (more than 5,000 pedigrees). Dyschromatopsia in males occurred in roughly one of 20 males, which is approximately the incidence in the United States. The second most common ocular disease was degenerative myopia, occurring in approximately one in 100 people. Congenital blepharoptosis occurred in one in 500; congenital cataract one in 3,000; retinitis pigmentosa in approximately one in 4,000; congenital glaucoma in one in 25,000; and congenital aniridia one in 130,000 people. Because the Chinese are a mixture of many racial groups, there are variations in incidence rates. For example, in the Miao race, the incidence of dyschromatopsia was only 1.75%, whereas in the Hasaka, a group that appears to be of Caucasian origin, the incidence of dyschromatopsia was 7.6%, almost identical to that in the western countries. The mode of inheritance of dyschromatopsia was x-linked recessive, as it is in other countries. In Leber's optic atrophy, the ratio of females to males in China was almost 50:50, whereas in western countries only about one sixth of the cases occur in females. Finally, it appears that closed-angle glaucoma is more common than open-angle glaucoma in China. (2 tables, 12 references)—David Shoch

Mayo Clinic Proceedings

Heparin therapy for recent transient focal cerebral ischemia. Keith, D. S., Phillips, S. J., Whisnant, J. P., Nishimaru, K., and O'Fallon, W. M. (Dept. Health Sci. Res., Mayo Clin., Rochester, MN 55905). Mayo Clin. Proc. 62:1101, 1987.

In a retrospective review of some 400 patients with initial episodes of transient ischemic attacks seen over a 25-year period, about 300 were examined within 30 days after the first attack. About one third were given heparin within 30 days after the first transient ischemic attack and about two thirds did not receive heparin. None of the patients had had a stroke before the initial examination for transient ischemic attacks. As might be expected, those with carotid disease had amaurosis fugax and other unilateral problems, whereas those with vertebrobasilar disease tended to have bilateral problems such as homonymous hemianopsia. There was no difference in age or sex between the group receiving heparin and that acting as a control. There was no statistically significant difference between the two groups for probability of survival, survival free from stroke, and survival free from transient ischemic attacks. The rate of hemorrhagic complications was 3.2 per 100 person-days of heparin therapy. The authors conclude as a result of their own study and studies in the literature that there is no real evidence to support the routine use of heparin as emergency therapy for patients with a history suggestive of recent transient ischemic attacks. (2 figures, 6 tables, 13 references)—David Shoch

Nature

Retinal pigmented epithelial cells induced to transdifferentiate to neurons by laminin. Reh, T. A., Nagy, T., and Gretton, H. (Neuroscience Res. Group, Dept. Med. Physiol., Univ. Calgary, Calgary, Alberta, Canada T2N 1N4). Nature 330:68, 1987.

The authors found that it is possible to generate retinal neurons from retinal pigment epithelial cells in retina if the cells are cultured on certain specific substrates. The most active substrate is laminin, a component of the extracellular matrix. When retinal pigment epithelial cells are plated on laminin, the cells undergo remarkable morphologic changes. Within one to three days the cells begin streaming toward one another and coalescing into clusters. Indirect immunofluorescent staining of these cells indicates that they are expressing a neuronal phenotype. Further, one third of the cells contain neurofilaments, a finding that is only true of retinal ganglion cells and not other retinal cell types. Thus, retinal regeneration can be initiated by changes in the composition of the extracellular matrix with which the retinal pigment epithelial cells come in contact. (2 figures, 1 table, 27 references)—David Shoch

New England Journal of Medicine

Potentiation by light of lithium-induced retinal injury in rats. Remé, C., Federspiel, E., Pfeilschifter, J., and Wirz-Justice, A. (Univ. Zurich, 8032 Zurich, Switzerland). N. Engl. J. Med. 317:1478, 1987.

Lithium carbonate was administered for three weeks in high and normal therapeutic doses to pigmented albino rats kept in a controlled light and dark cycle with a low light intensity. Severe destruction of lipoprotein outer segment membranes of retinal photoreceptors with fairly high levels of lithium in the retina were noted. When the dark-adapted animals were exposed to acute pulses of light of increasing intensity there was a dramatic increase in the effect of lithium, which was dependent on the intensity. The authors advised evaluation of retinal function in patients receiving long-term treatment with lithium. (1 figure, 8 references)—David Shoch

Infection of the retina by human immunodeficiency virus type I. Pomerantz, R. J., Kuritzkes, D. R., de la Monte, S. M., Rota, T. R., Baker, A. S., Albert, D., Bor, D. H., Feldman, E. L., Schooley, R. T., and Hirsch, M. S. (Infect. Dis. Unit, Massachusetts Gen. Hosp., Boston, MA 02114). N. Engl. J. Med. 317:1643, 1987.

The retinas were obtained in two patients with the acquired immunodeficiency syndrome, one of whom died of brain and meningeal infection with *Cryptococcus neoformans* and the other of whom developed a central nervous system plasmacytoid lymphoma, and were cultured for the presence of immunodeficiency virus. The virus was detected in the retina of the first patient after seven days. Cytomegalovirus was not found but *Cryptococcus neoformans* was also recovered from fungal cultures of the retina. In the second patient the human immunodeficiency virus was isolated after ten days of culture, although only cotton-wool spots had been noted during the patient's lifetime. Thus, there is evidence that in addition to opportunistic infection the retina may also be host to the human immunodeficiency virus. (2 figures, 47 references)—David Shoch

Pediatrics

Neonatal anesthesia. Poland, R. L., Roberts, R. J., Gutierrez-Mazorra, J., and Fonkalsrud, E. W. Pediatrics 80:446, 1987.

It has been common practice to perform certain examinations and surgical procedures on unanesthetized neonates under the rationale that the risk of anesthesia is too great to justify the possible benefit of pain relief. The chairmen of several committees of the American Academy of Pediatrics have concluded that, in light of new pharmacologic agents and information now available, it is safe to administer anesthesia or analgesia to neonates undergoing diagnostic or surgical procedures. The administration should follow the usual guidelines for administration of anesthesia to high-risk, potentially unstable patients. The decision to use or withhold a particular medication for neonates should be based on the same medical criteria as for older patients. (12 references)—Paul E. Romano

NEWS ITEMS

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The Journal invites information concerning meetings, postgraduate courses, lectures, honors, and appointments. Double space each item and provide the name and address of the responsible author. Announcements of courses, meetings, and lectures must be submitted at least six months before the date of the event.

Minnesota Academy of Ophthalmology: Nineteenth Annual William L. Benedict Lecture

The Minnesota Academy of Ophthalmology presented the Nineteenth Annual William L. Benedict Memorial Lecture at its meeting Jan. 8, 1988. Richard F. Hanson, Director of the Gray Freshwater Biological Institute, was the guest speaker. Dr. Benedict was president of the Ophthalmic Publishing Company at the time of his death in 1969.

International Conference on Ophthalmic Photography

The Ophthalmic Photographers' Society will hold an International Conference on Ophthalmic Photography, March 12–15, 1988, in Singapore. For further information, write Lawrence M. Merin, R.B.P., Meeting Chairman, c/o Cullen Eye Institute, Baylor College of Medicine, 6501 Fannin, Houston, TX 77030.

New Developments in Ophthalmology 1988

New Developments in Ophthalmology 5 will be held Sept. 1–3, 1988, in Nijmegen, The Netherlands. For further information, write Prof. Dr. A. F. Deutman, University Hospital, Dept. of Ophthalmology, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

Eye Hospital Rotterdam: Third Course on Silicone Oil in Vitreoretinal Surgery

The Eye Hospital Rotterdam will sponsor the Third Course on Silicone Oil in Vitreoretinal Surgery Sept. 12 and 13, 1988. For further information, write Dorine Verhoeven, Course Secretary, Eye Hospital Rotterdam, Schledamsevest 180, 3000 LM Rotterdam, The Netherlands.

American Society of Ophthalmic Plastic and Reconstructive Surgery: 1988 Officers

The American Society of Ophthalmic Plastic and Reconstructive Surgery elected the following officers for 1988 at the metting of the society in Dallas: Arthur J. Schaefer, president; Clinton D. McCord, Jr., president-elect; Richard L. Anderson, vice-president; William B. Stewart, executive secretary; John A. Burns, treasurer; Richard K. Dortzback, secretary; Daniel L. McLachlan, program chairman; and Ralph E. Wesley, assistant program chairman.

American Society of Ophthalmic Plastic and Reconstructive Surgery: Annual Meeting

The American Society of Ophthalmic Plastic and Reconstructive Surgery will hold its annual meeting, Oct. 7, 1988, in Las Vegas, Nevada. For further information, write Daniel L. McLachlan, M.D., 122 S. Michigan Ave., Suite 1427, Chicago, IL 60603.

Cleveland Clinic Foundation: Continuing Education Program

The Cleveland Clinic Foundation is sponsoring a continuing education program, Ophthalmology, June 17 and 18, 1988, in Bunts Auditorium at the Cleveland Clinic. For further information, write Department of Continuing Education, Cleveland Clinic Educational Foundation, 9500 Euclid Ave., Room TT3-301, Cleveland, OH 44195; telephone (800) 762-8173 (national), (800) 762-8173 (Ohio), or (216) 444-5695.

Doheny Eye Institute: Retina for the Cataract Surgeon

The Doheny Eye Institute will sponsor a course, Retina for the Cataract Surgeon, June 18, 1988, in Los Angeles, California. For further information, write Laurie Woolf, Continuing Medical Education, Doheny Eye Institute, 1355 San Pablo St., Los Angeles, CA 90033.

Jules Stein Eye Institute: Nineteenth Jules Stein Lecture

The Nineteenth Jules Stein Lecture will be given by Arthur J. Jampolsky, April 22, 1988, in Los Angeles, California. The annual postgraduate seminar will be held April 23, 1988. For further information, write Wrennie Murphy, Director of Academic Programs, Jules Stein Eye Institute, UCLA Medical Center, Los Angeles, CA 90024.

Long Island Jewish Medical Center: A Clinical Day in Ophthalmology: Pediatric Topics

The Department of Ophthalmology, Long Island Jewish Medical Center, and the Division of Ophthalmology, North Shore University Hospital, will co-sponsor a course, A Clinical Day in Ophthalmology: Pediatric Topics, March 30, 1988, at the Garden City Hotel, Garden City, New York. The tuition is $150; $75 for residents or fellows and it includes lunch and coffee break. The faculty includes John Flynn, Creig Hoyt, and David Walton. For further information, write Ann J. Boehme, CMP Associate Director for Continuing Education, Long Island Jewish Medical Center, New Hyde Park, NY 11042; telephone (718) 470-8650.

Manhattan Eye, Ear and Throat Hospital: Vitrectomy Course

The Manhattan Eye, Ear and Throat Hospital will hold a symposium, Vitrectomy in Anterior and Posterior Segment Surgery, June 4, 1988, in New York, New York. For further information, write Martha Klapp, Department of Ophthalmology, Manhattan Eye, Ear and Throat Hospital, 210 E. 64th St., New York, NY 10021.

National Eye Institute: Clinical Vision Research: Epidemiologic and Biostatistical Approaches

The National Eye Institute will sponsor the Ninth Annual Course for vision researchers, "Clinical Vision Research: Epidemiologic and Biostatistical Approaches," April 28–May 1, 1988, at Longboat Key Club, Longboat Key, Florida. For further information, write Catherine M. Beinhauer, Conference Management Associates, Inc., 127 Brook Hollow, Hanover, NH 03755; telephone (603) 643-2325.

Ohio State University: Eighth Annual Resident Alumni Research Symposium

The Department of Ophthalmology of Ohio State University will hold its Eighth Annual Resident Alumni Research Symposium June 11, 1988. For more information, write Maureen A. Meck, Symposium Coordinator, Ohio State University, Department of Ophthalmology, 456 W. 10th Ave., Columbus, OH 43210; telephone (614) 293-8159.

University of Toronto: 30th Annual Research Meeting and Eighth Clement McCulloch Lecture

The Department of Ophthalmology of the University of Toronto will hold the 30th Annual Research Meeting and the Eighth Clement McCulloch Lecture at the Addiction Research Foundation, Toronto, April 8, 1988. The guest speaker is David A. Robinson, Professor of Ophthalmology, Johns Hopkins Hospital. The title of his lecture is Signal Processing in the Oculomotor System. For more information, write Dr. G. E. Trope, Department of Ophthalmology, Toronto General Hospital, Eaton Building, 5-308, Toronto, Ontario M5G 2C4; telephone (416) 595-3580.

University of Washington: Fourteenth Annual Resident Alumni Day

The University of Washington will hold the Fourteenth Annual Resident Alumni Day, May 21, 1988, in Seattle, Washington. For further information, write Richard P. Mills, M.D., Department of Ophthalmology, University of Washington, (RJ-10), Seattle, WA 98195.

Joint Commission on Allied Health Personnel in Ophthalmology: Certification Examinations for Ophthalmic Medical Assistants

Applications are available through March 25, 1988, for the Joint Commission on Allied Health Personnel in Ophthalmology certification examinations for ophthalmic medical assistants. The written examinations at three skill levels will be held July 8, 1988, at more than 60 locations throughout the United States. Applications for the written certifying examinations must be received by March 30, 1988. For further information, write Joint Commission on Allied Health Personnel in Ophthalmology, 1812 N. St. Paul Rd., St. Paul, MN 55109; telephone (800) 284-3937, (612) 770-9775.

Tulane Medical Center: Tulane-Ellender Contact Lens Course

Tulane University Medical Center will sponsor the Tulane-Ellender Contact Lens Course, April 29 and 30, 1988, in New Orleans, Louisiana. For further informaton, write J. A. D'Angelo, Jr., Tulane Medical Center, Office of Continuing Education, Tulane University, 1430 Tulane Ave., New Orleans, LA 70112.

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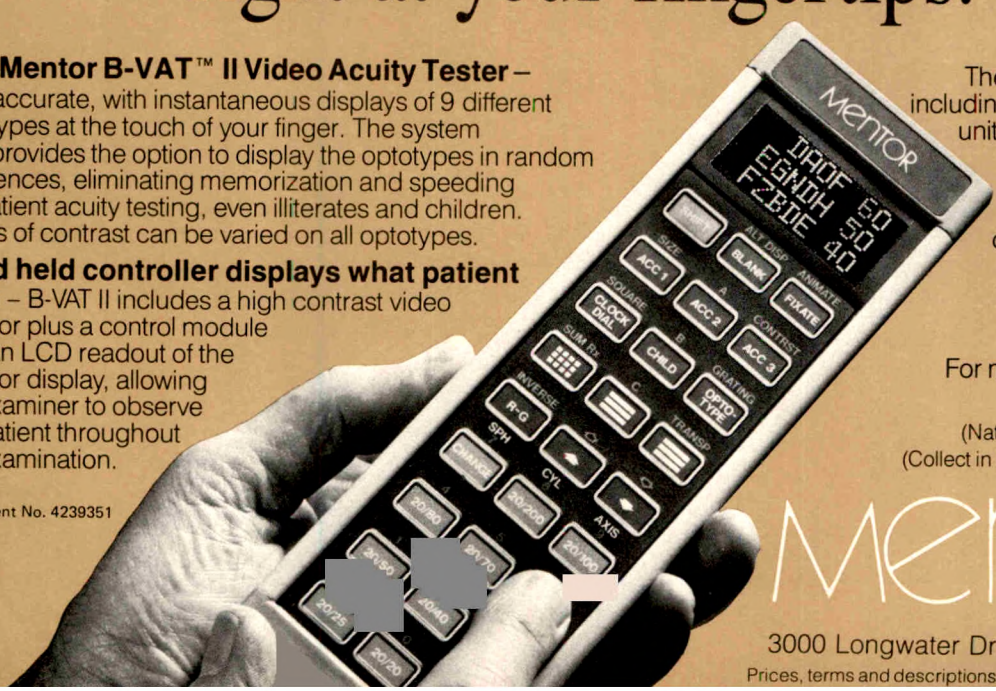


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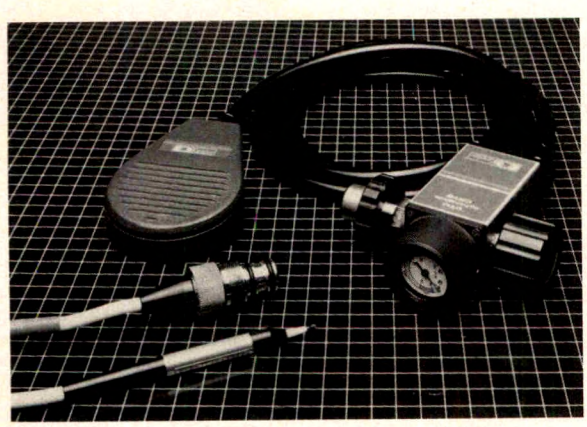
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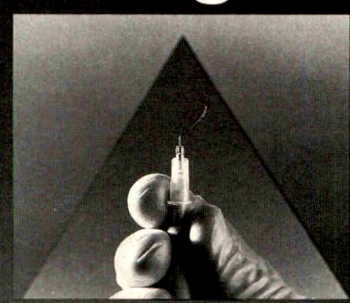
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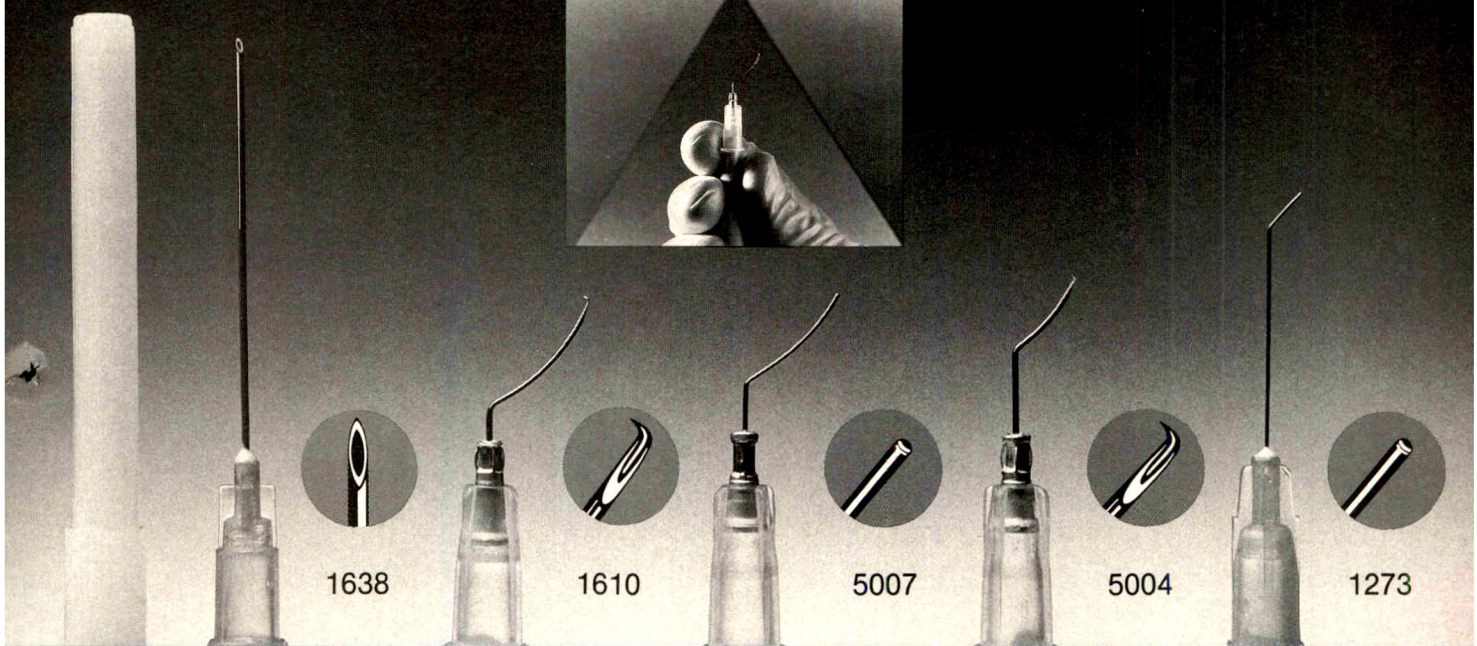
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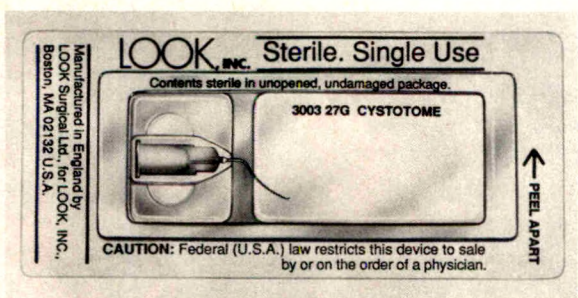
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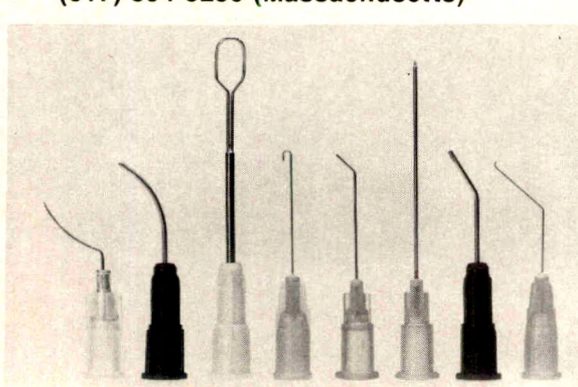
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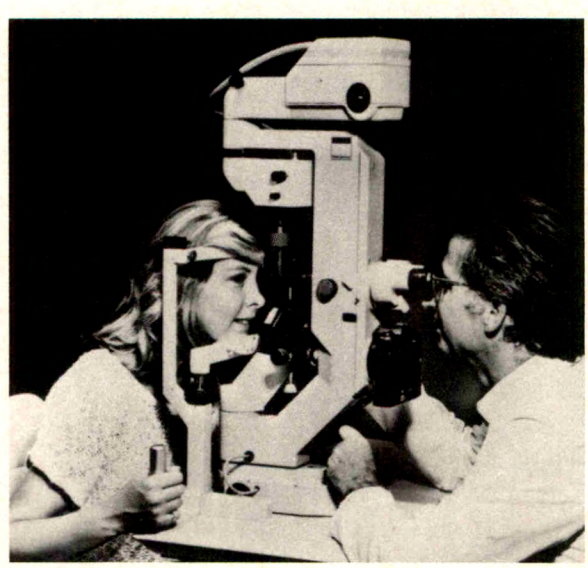
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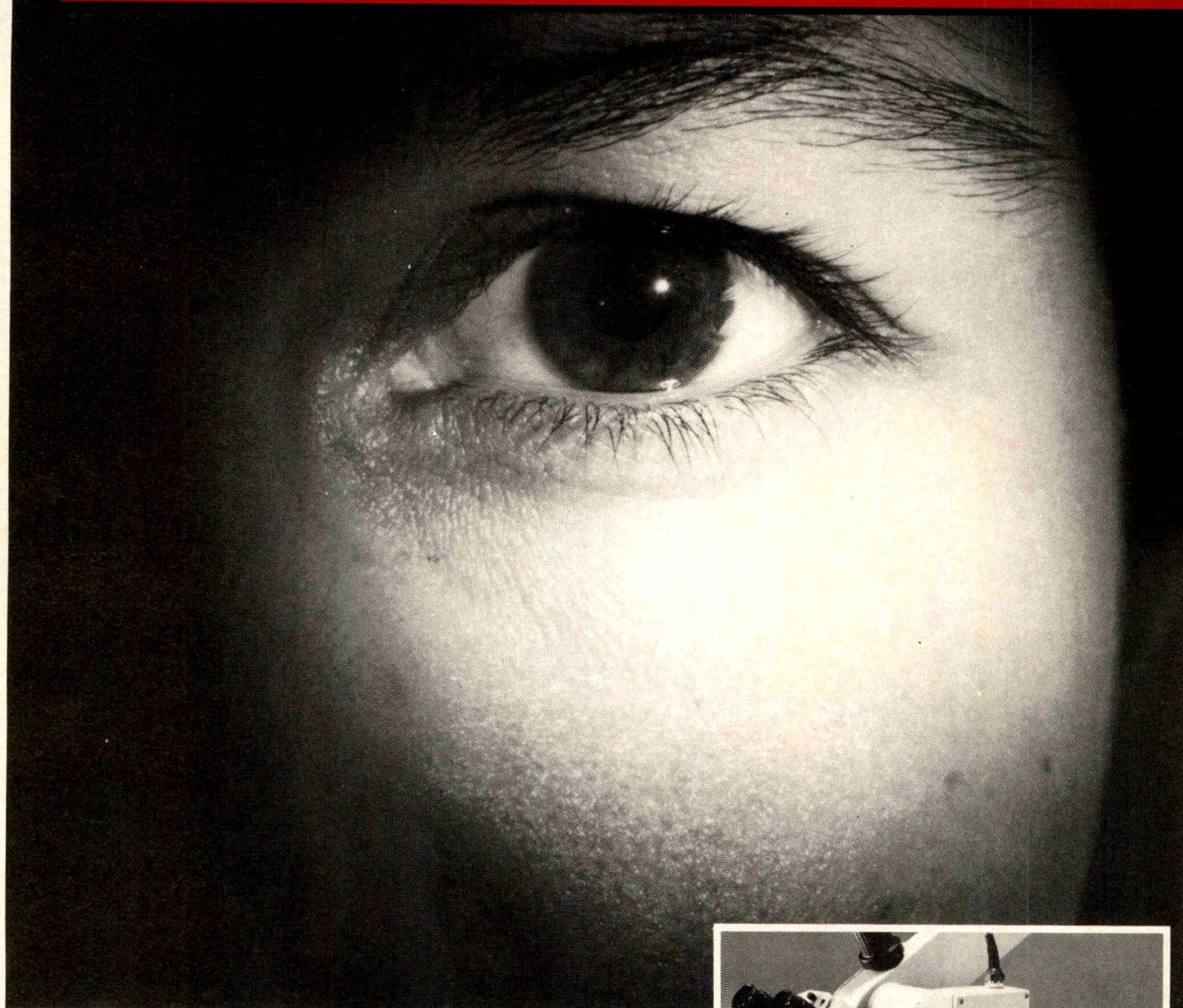
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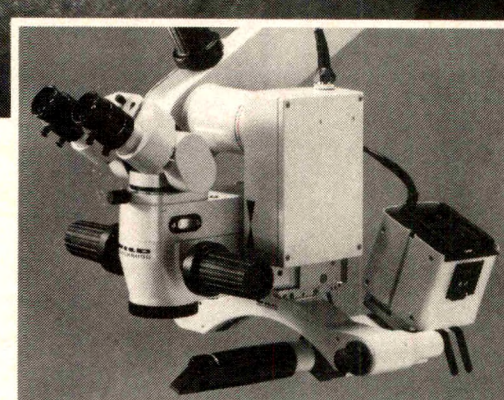
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The new Zeiss Photo Slit Lamp 40 SL/P for hospitals and physicians' offices allows the user to perform every type of slit photography with one instrument. Designed for photodocumentation and diagnosis of ocular anterior segment diseases, the 40 SL/P Photo Slit Lamp permits motorized setting of the slit width and height. The adjustable slit depth of focus lets the clinician transect the anterior segment in one optical slit, with the option to set double or triple slit for safer, faster diagnosis.

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Tel: (800) 843-1137

IntraOptics, Inc. has acquired the rights to the product line for the Opacity Lensmeter, developed by the Swiss engineering firm Interzeag. The Opacity Lensmeter can detect objectively and quantify the slightest degree of opacity or cataract present. It provides the physician with a precise, documented measurement of opacity. The Opacity Lensmeter provides adequate and accurate documentation for Medicare, legal, clinical, and ethical purposes.

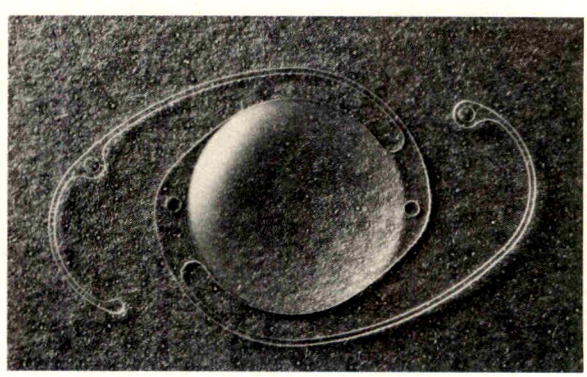
Intraocular Lenses

3M Vision Care
P.O. Box 33600
St. Paul, MN 55133-3600
Tel: (800) 235-6911 (National)
(800) 322-6981 (California)

3M Vision Care has introduced an all polymethylmethacrylate intraocular lens with Easy-Flex brand haptics. The haptic features a flex point designed to permit flexibility for ease of insertion. The Style 15LE modified C-loop lens, for surgical correction of aphakia after extracapsular cataract extraction, features 5/0 blue PMMA haptics designed specifically to overcome the stiffness often associated with PMMA loops.

The lens is designed for laser use. Having no ridge, for maximum usable optic area, the convex-concave 6-mm optic with full-range ultraviolet absorption is available in powers ranging from 9.0 to 25.0 diopters in 1.0 diopter increments, and from 14.5 to 24.5 diopters in 0.5 diopter increments. Optics are available either with four 0.4-mm positioning holes or without holes, for glare reduction. This is an investigational device.

Optical Radiation Corp.
1300 Optical Dr.
Azusa, CA 91702
Tel: (800) 423-1887 (National)
(800) 821-8754 (California)



Optical Radiation Corp. has introduced the U150KC, a one-piece polymethylmethacrylate, plano convex posterior chamber lens. The lens has a full 6.0-mm functional optic zone, with two positioning holes at the 6 and 12 o'clock meridians on the gussets and two eyelets. The haptic design minimizes pressure on eye tissues. The lens has excellent centration, thus reducing the potential for glare.

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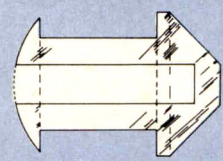
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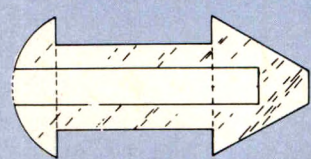
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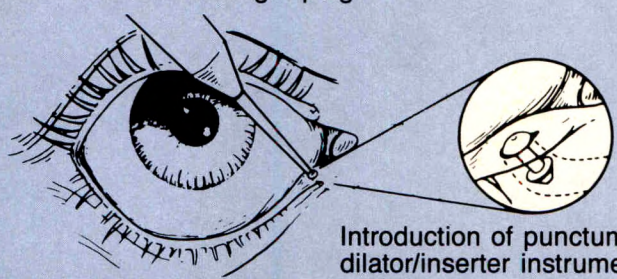
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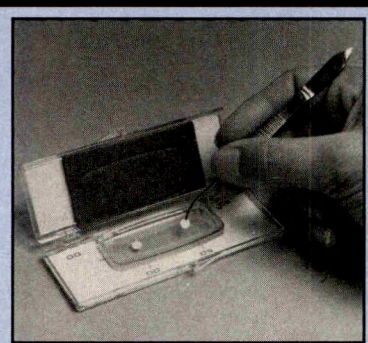
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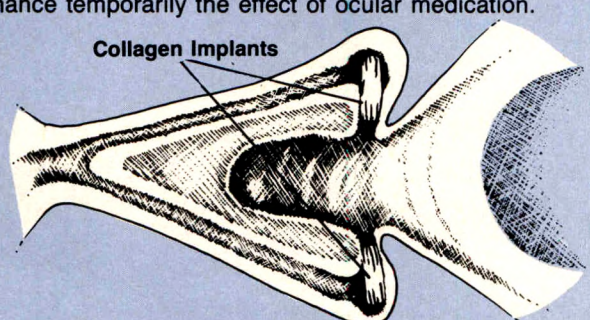
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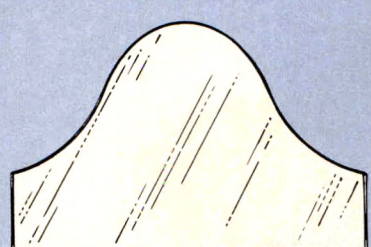
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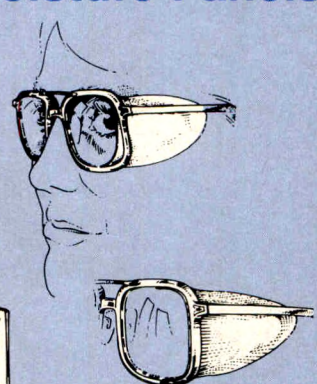
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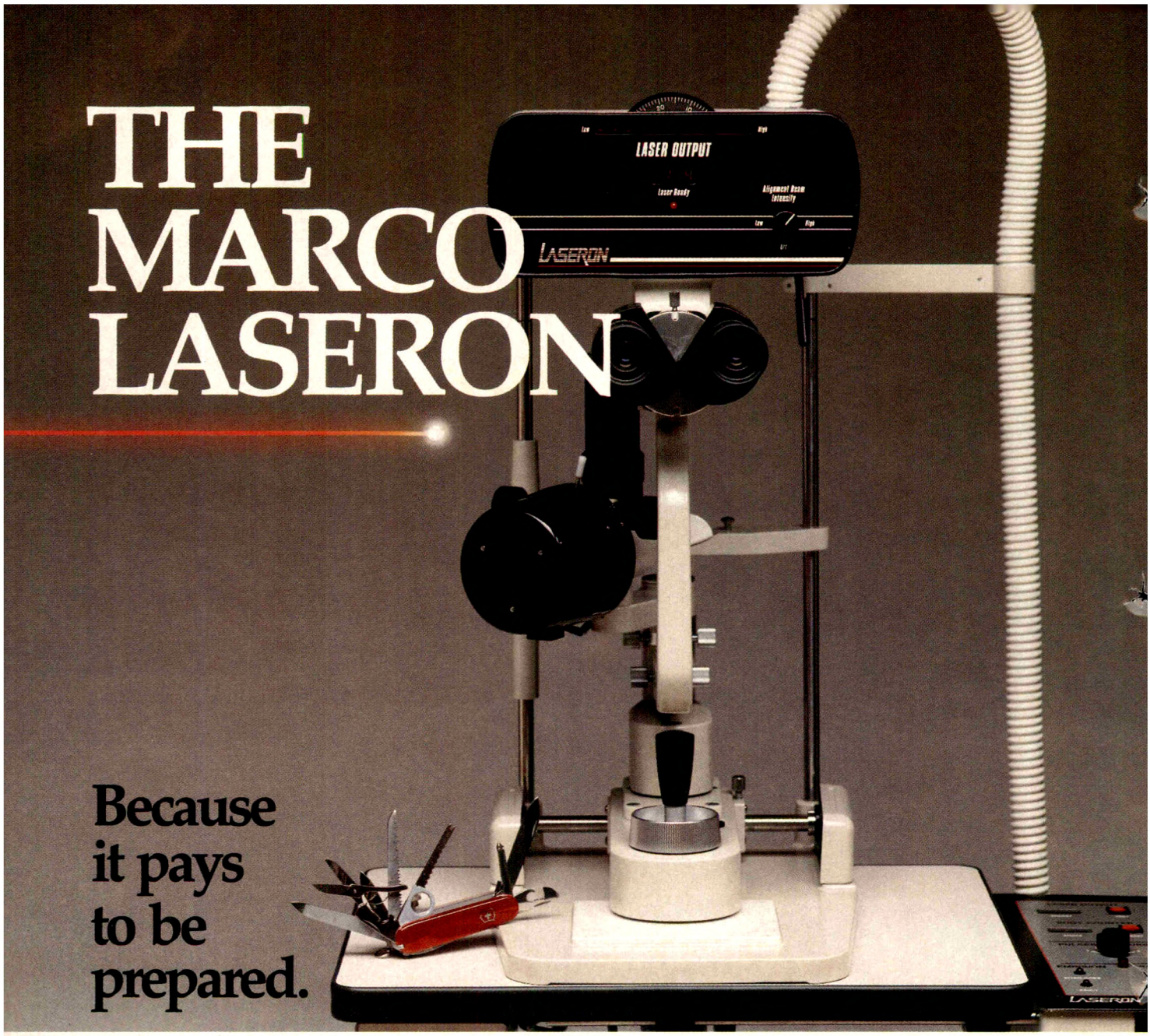
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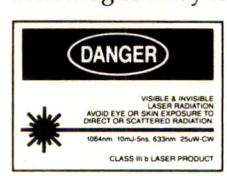
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Unusual Central Chorioretinitis as the First Manifestation of Early Secondary Syphilis

Eduardo Cunha de Souza, M.D., Alex E. Jalkh, M.D., Clement L. Trempe, M.D., Sergio Cunha, M.D., and Charles L. Schepens, M.D.

Three young, otherwise healthy patients had a similar picture of unilateral central chorioretinitis associated with severe visual loss. Fluorescein angiography disclosed diffuse leakage under the neurosensory retina in the posteror pole, associated with multifocal areas of staining along the retinal vessels. Systemic examination showed a positive fluorescent treponemal antibody absorption test and a sharp increase in VDRL titers, indicative of active secondary syphilis. The patients responded dramatically to penicillin treatment, with visual recovery and resolution of the fundus lesions.

© American Journal of Ophthalmology 105:271–276, March, 1988

Anterior Proliferative Vitreoretinopathy

Hilel Lewis, M.D., and Thomas M. Aaberg, M.D.

During a four-year period, 53 of 92 eyes (58%) undergoing vitreoretinal surgery for a retinal detachment with proliferative vitreoretinopathy demonstrated anterior proliferative vitreoretinopathy. We classified anterior proliferative vitreoretinopathy according to tractional direction, location, extent, and severity. Initially, the eyes were treated with a high scleral buckle and laser endophotocoagulation as an adjunct to vitrectomy. Treatment then evolved into a direct approach in which the anterior proliferative tissue was surgically cut or excised. Of the 42 eyes followed up for at least six months, 25 (59%) were totally reattached and 18 (43%) had a visual acuity of 5/200 or better.

© American Journal of Ophthalmology 105:277–284, March, 1988

The Pathogenesis of Tears of the Retinal Pigment Epithelium

Elaine L. Chuang, M.D., and Alan C. Bird, M.D.

We compared drusen in the fellow eye of patients with unilateral retinal pigment epithelial tears with those in an age- and sex-matched group of patients with unilateral primary neovascular disciform lesions. In the fellow eye of patients with tears, drusen were more confluent and manifested less fluorescence on angiography than in the comparison group. These observations are in accord with the concept that Bruch's membrane represents a significant barrier to fluid flow, and that fluid beneath detached pigment epithelium is derived in part or wholely from the pigment epithelium.

© American Journal of Ophthalmology 105:285–290, March, 1988

Pigmentary Changes in Acquired Retinoschisis

Mark DiSclafani, M.D., Alan Wagner, M.D., William Humphrey, M.D., and James Valone, Jr., M.D.

We reviewed retrospectively the records of patients referred for retinal examination and found 375 eyes (233 patients) with acquired retinoschisis. Of the 375 eyes, 85 had outer layer retinal breaks, 27 had retinal detachments, and 29 had pigmentary lines. Twenty-five of the 29 pigmentary lines (86.2%) demarcated either retinal detachment or outer retinal layer breaks.

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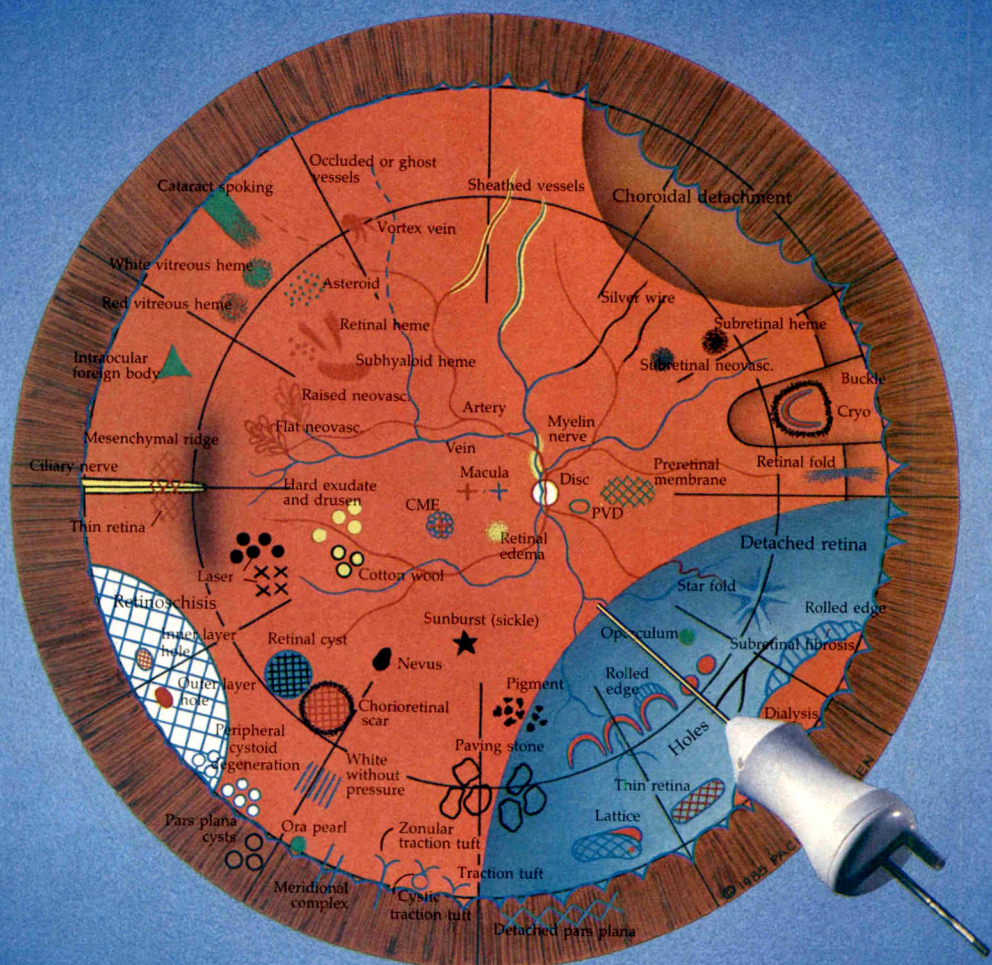
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Leukemic Involvement of the Optic Nerve

Hirotoshi Nikaido, M.D., Hiromu Mishima, M.D., Hideyuki Ono, M.D., Kanji Choshi, M.D., and Hiroo Dohy, M.D.

We studied five cases of leukemia with invasion of the optic disk and optic nerve. Two patients had acute lymphoblastic leukemia and three had acute myelogenous leukemia. All patients received intrathecal injections of chemotherapeutic drugs including methotrexate, cytarabine, and prednisolone. Three patients underwent irradiation therapy of the whole brain and optic nerve. While initial improvement in the ophthalmic abnormalities, such as optic disk edema, flame-shaped retinal hemorrhages, and dilation of the retinal vein, was noted, optic atrophy was later found in all eyes.

© American Journal of Ophthalmology 105:294–298, March, 1988

A Long-Term Follow-up Study of Laser Coagulation of Neovascular Membranes in Angioid Streaks

Ö. Gelisken, M.D., F. Hendrikse, M.D., and A. F. Deutman, M.D.

We treated 30 eyes (24 patients) with angioid streaks and neovascular membranes using light coagulation. Of 30 eyes, 16 showed either ameliorated or unchanged visual acuity. Twelve of the remaining 14 eyes retained a visual acuity of 20/200 or better. In 11 patients, the fellow untreated eye showed central macular degeneration with loss of central vision. The follow-up period ranged from two months to 16 years (mean, 3.4 years).

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Fadenoperation for the Management of Complicated Incomitant Vertical Strabismus

Edward G. Buckley, M.D., and Bettina B. Meekins, M.D.

We reviewed retrospectively the records of 17 patients with incomitant vertical diplopia secondary to an underacting inferior rectus muscle who had been treated by surgically weakening the contralateral inferior rectus muscle with a posterior fixation suture (fadenoperation). This was the sole procedure in four patients with blowout fractures and in two patients with restriction secondary to scleral buckling procedures. It was combined with horizontal or vertical muscle surgery in 11 patients. The procedure was particularly useful in preventing diplopia on downgaze after excessive weakening of a tight inferior rectus muscle in seven patients with thyroid ophthalmopathy. In three patients it was used in anticipation of an iatrogenic incomitancy in downgaze secondary to a large recession of a tight inferior rectus muscle. All patients were markedly improved after surgery and no complications were encountered.

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Negative Antibody Response to Long-Term Treatment of Facial Spasm With Botulinum Toxin

Russell S. Gonnering, M.D.

Over a period of 163 weeks, 223 injections of botulinum A toxin were administered to 38 patients with facial spasm syndromes. The maximum cumulative toxin dose was 553 units, the maximum number of injections in any given patient was 16, and the maximum dosage of any given injection was 52.5 units. Sera from these patients showed no antibody production when measured with a standard mouse lethality bioassay.

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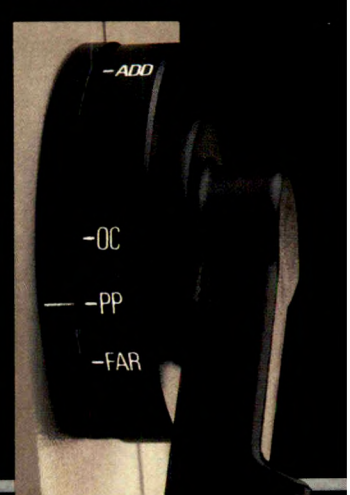
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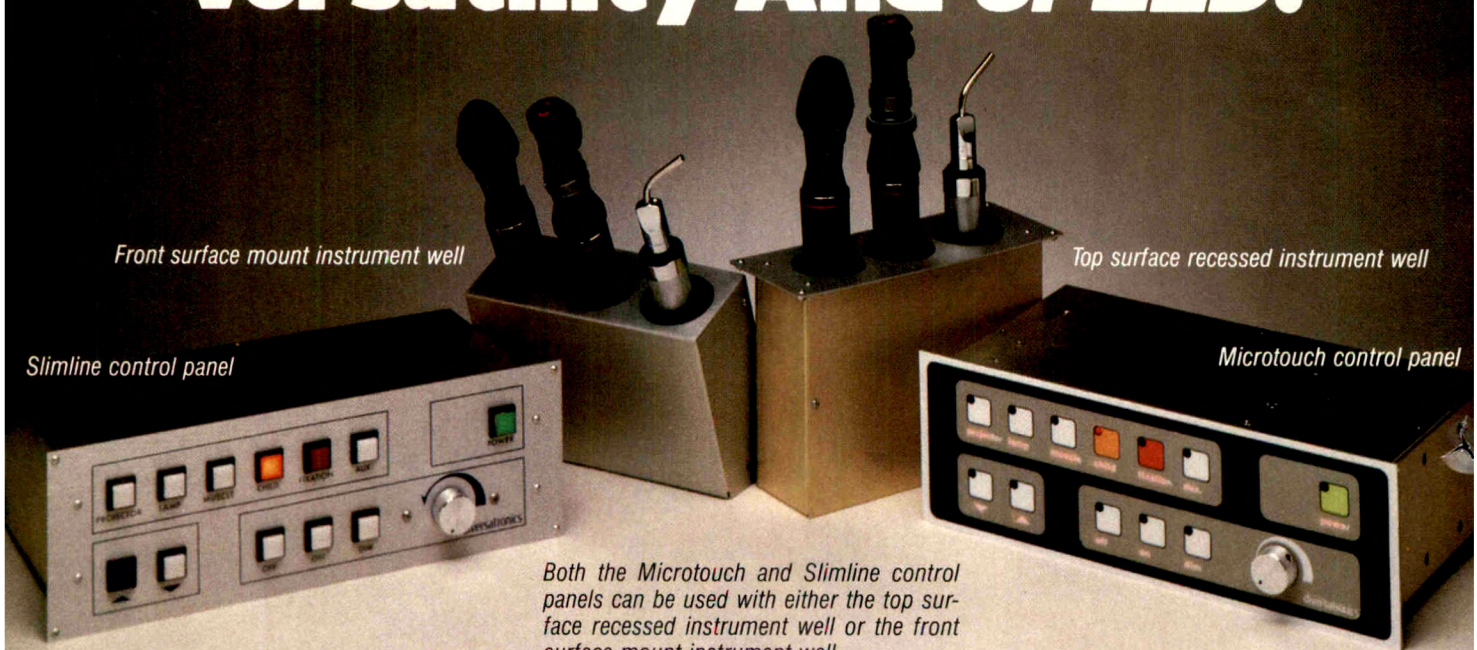
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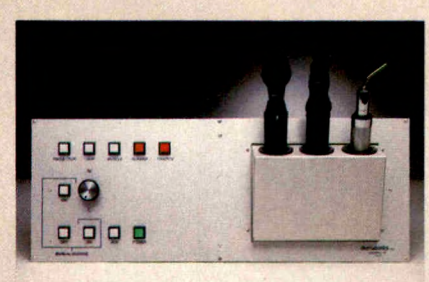
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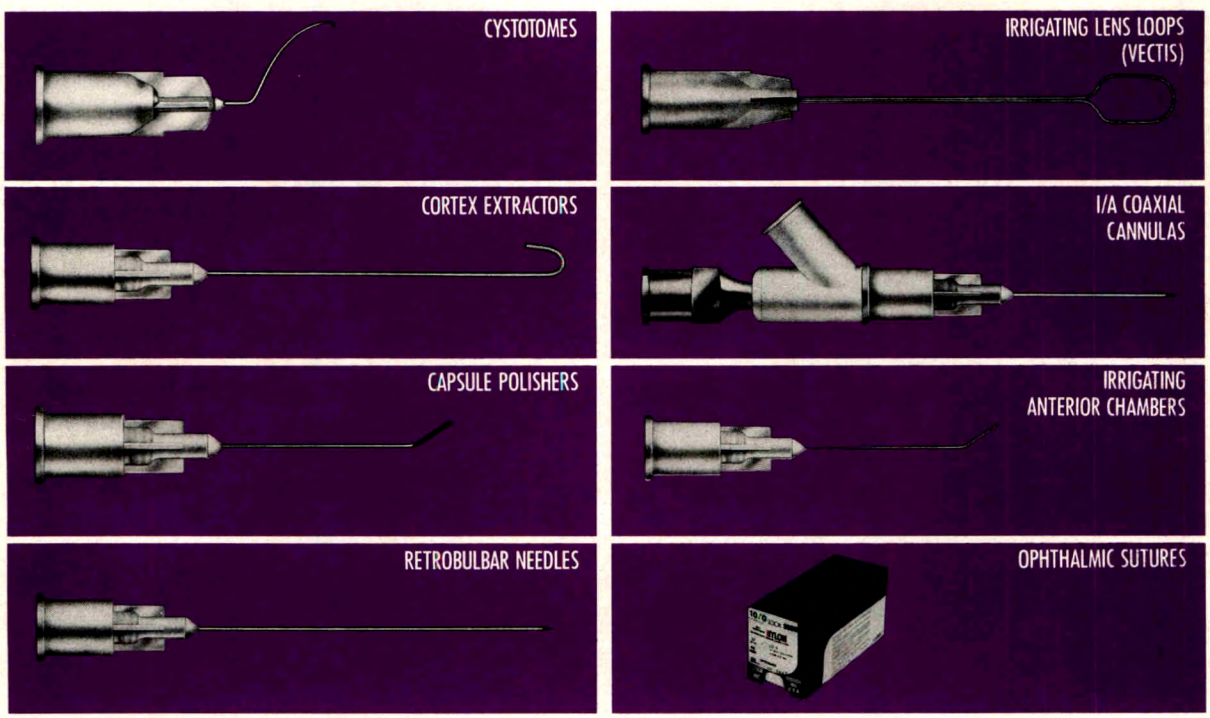
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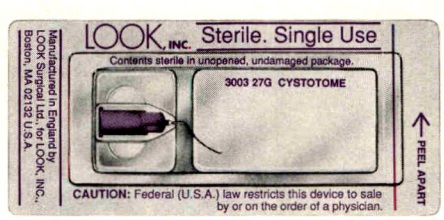
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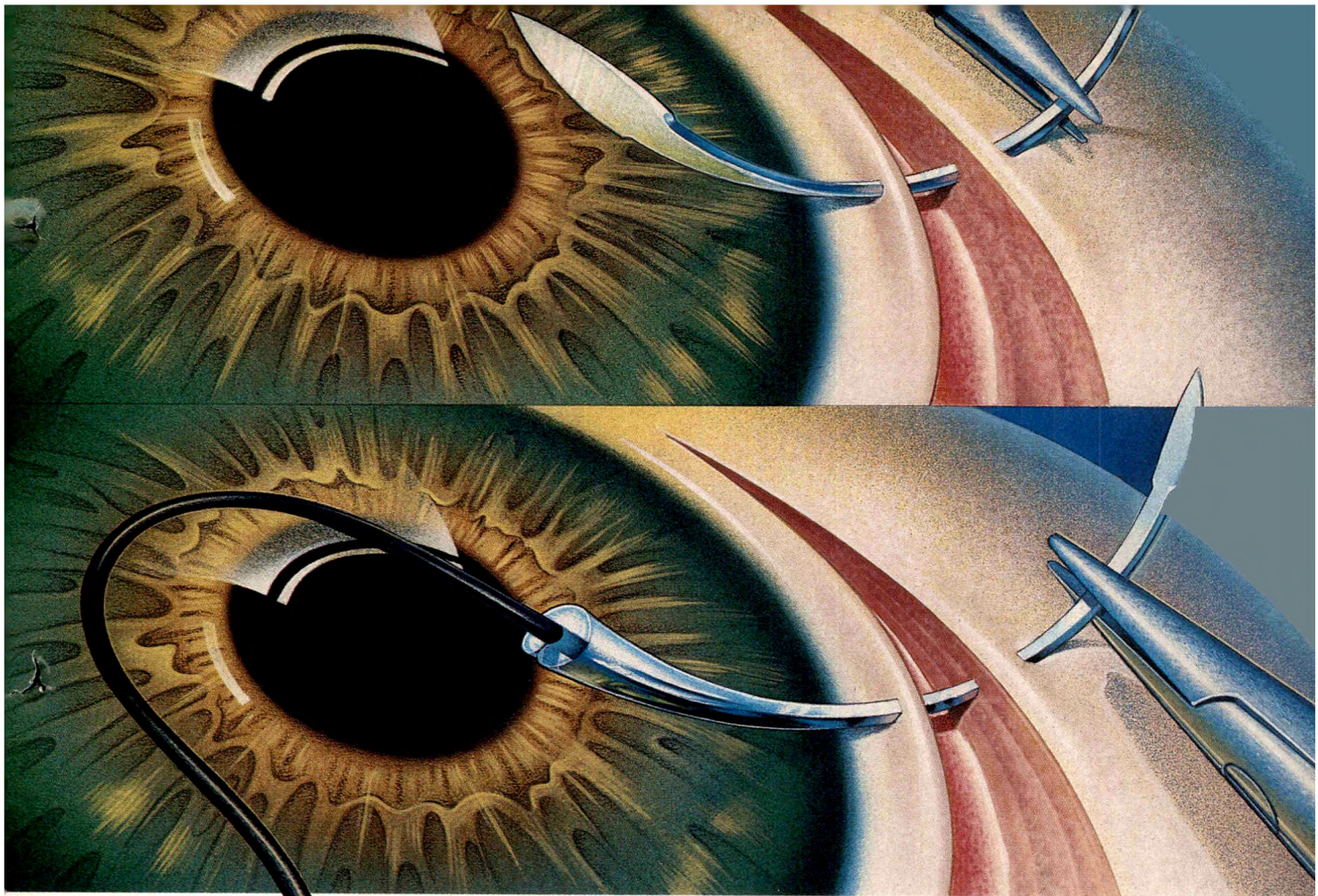
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Glaucoma
Pediatrics
Ophthalmic Pathology

Duties will include clinical and academic responsibilities in a variety of settings. Academic rank and salary will be discussed in relation to qualifications. Please send inquiries to the attention of:

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Professor and Chairman
Department of Ophthalmology
Emory University School of Medicine
1327 Clifton Road, N.E.
Atlanta, Georgia 30322

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Send Curriculum Vitae and names of three referrees to:

Michael F. Marmor, M.D.
Professor and Acting Chairman
Department of Ophthalmology, A157
Stanford University Medical Center

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The Department of Ophthalmology, Jules Stein Eye Institute, and the Doris Stein Eye Research Center, University of California, Los Angeles, (UCLA), School of Medicine are seeking applicants for a faculty position in Vitreoretinal Disease and Surgery. Individuals dedicated to a career in vision research, teaching, and ophthalmic patient care are encouraged to apply. The Search Committee is specifically seeking a qualified ophthalmologist with a strong background in surgery and medical retina research, vitreoretinal surgery and ophthalmic pathology research. Expertise and research experience are required in vitreoretinal diseases, diabetic vitrectomy, proliferative vitreoretinopathy, and age-related macular degeneration. Annual salary level from $100,000 to $200,000. Applications including curriculum vitae, bibliography, and a letter discussing career goals should be sent to:

Allan Kreiger, M.D.
Chair, Vitreoretinal Search Committee
Jules Stein Eye Institute
UCLA School of Medicine
Los Angeles, CA 90024

All applications and inquiries will be treated in strict confidence. Candidates are encouraged to apply regardless of gender or ethnic origin. UCLA is an Equal Opportunity Affirmative Action Employer.

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Indiana University is an Equal Opportunity and Affirmative Action Employer. Send C.V., and list of references to:

Robert Yee, M.D.
c/o Sandra Eads
Indiana University
Department of Ophthalmology
702 Rotary Circle
Indianapolis, Indiana 46223

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Boston University School of Medicine Department of Ophthalmology

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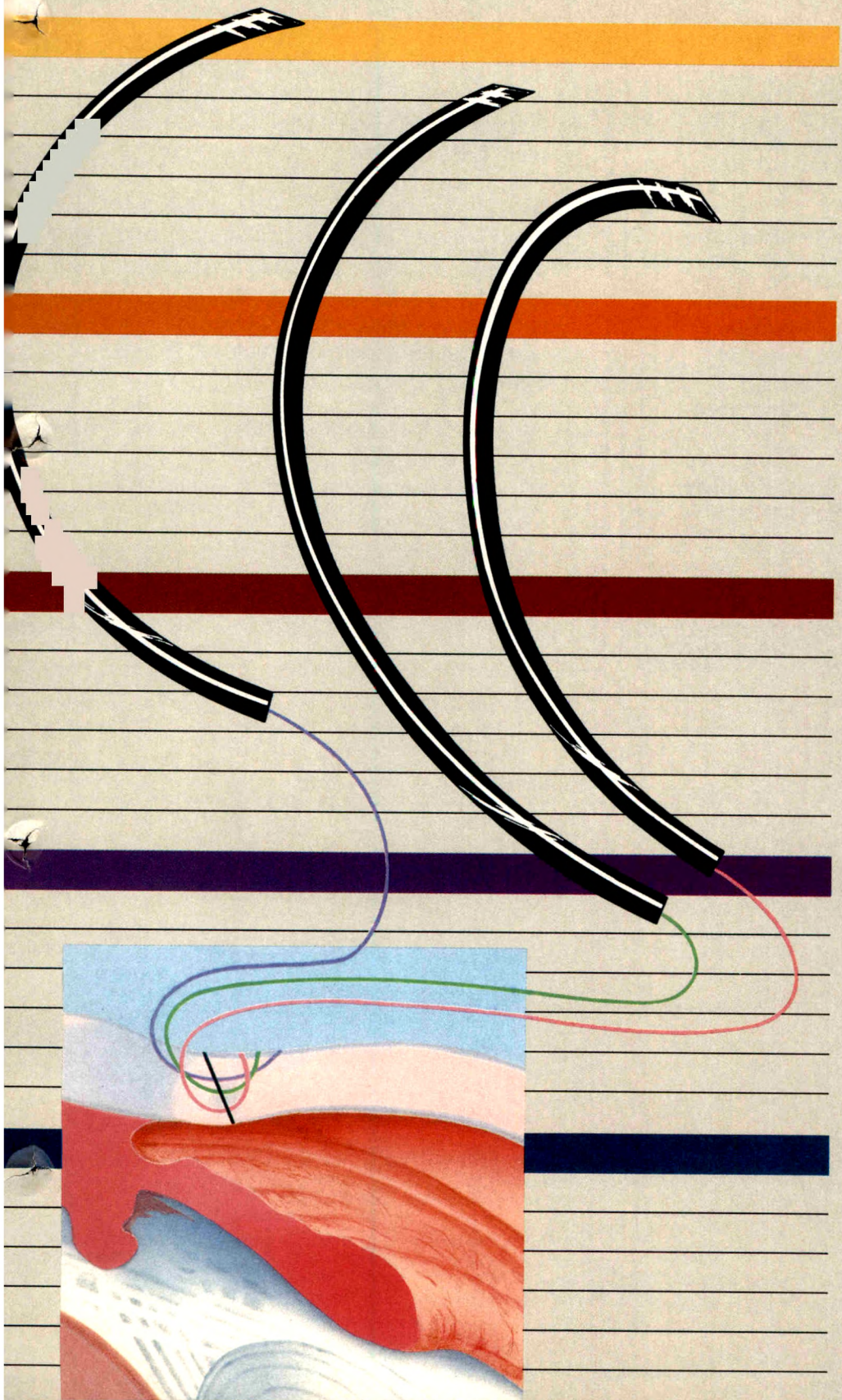
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OPHTHALMOLOGY PRACTICE FOR SALE: Solo general ophthalmology practice for sale. Located in the San Francsico Bay Area (Berkeley, California). Starting date open—Spring of 1988. Box 005 AJO.

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ACTIONS
Prednisolone acetate is a glucocorticoid that, on the basis of weight, has 3 to 5 times the anti-inflammatory potency of hydrocortisone. Glucocorticoids inhibit the edema, fibrin deposition, capillary dilatation and phagocytic migration of the acute inflammatory response as well as capillary proliferation, deposition of collagen and scar formation.

INDICATIONS
For steroid responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe.

CONTRAINDICATIONS
Acute untreated purulent ocular infections, acute superficial herpes simplex (dendritic keratitis), vaccinia, varicella and most other viral diseases of the cornea and conjunctiva, ocular tuberculosis and fungal diseases of the eye, and sensitivity to any components of the formulation.

WARNINGS
1. In those diseases causing thinning of the cornea, perforation has been reported with the use of topical steroids.
2. Since PRED FORTE contains no antimicrobial, if infection is present appropriate measures must be taken to counteract the organisms involved.
3. Acute purulent infections of the eye may be masked or enhanced by the use of topical steroids.
4. Use of steroid medication in the presence of stromal herpes simplex requires caution and should be followed by frequent mandatory slit lamp microscopy.
5. As fungal infections of the cornea have been reported coincidentally with long-term local steroid applications, fungal invasion may be suspected in any persistent corneal ulceration where a steroid has been used, or is in use.
6. Use of topical corticosteroids may cause increased intraocular pressure in certain individuals. This may result in damage to the optic nerve with defects in the visual fields. It is advisable that the intraocular pressure be checked frequently.
7. **Use in Pregnancy**—Safety of intensive or protracted use of topical steroids during pregnancy has not been substantiated.

PRECAUTIONS
Posterior subcapsular cataract formation has been reported after heavy or protracted use of topical ophthalmic corticosteroids.

Patients with histories of herpes simplex keratitis should be treated with caution.

ADVERSE REACTIONS
Increased intraocular pressure, with optic nerve damage, defects in the visual fields. Also posterior subcapsular cataract formation, secondary ocular infections from fungi or viruses liberated from ocular tissues, and perforation of the globe when used in conditions where there is thinning of the cornea or sclera. Systemic side effects may occur with extensive use of steroids.

DOSAGE AND ADMINISTRATION
1 to 2 drops instilled into the conjunctival sac two to four times daily. During the initial 24 to 48 hours the dosage may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely.

NOTE: Keep this and all medications out of the reach of children.

HOW SUPPLIED
As a sterile suspension in 1 mL, 5 mL, 10 mL and 15 mL plastic dropper bottles. On prescription only.

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INFLAMASE FORTE Ophthalmic Solution is recommended for moderate to severe inflammations, particularly when unusually rapid control is desired. In stubborn cases of anterior segment eye disease, systemic adrenocortical hormone therapy may be required. When the deeper ocular structures are involved, systemic therapy is necessary. ■ **CONTRAINDICATIONS:** The use of these preparations is contraindicated in the presence of acute superficial herpes simplex keratitis, fungal diseases of the ocular structures, acute infectious stages of vaccinia, varicella and most other viral diseases of the cornea and conjunctiva, tuberculosis of the eye and hypersensitivity to a component of this preparation. • The use of these preparations is always contraindicated after uncomplicated removal of a superficial corneal foreign body. ■ **WARNINGS:** Employment of steroid medication in the treatment of herpes simplex keratitis involving the stroma requires great caution; frequent slit lamp microscopy is mandatory. • Prolonged use may result in elevated intraocular pressure and/or glaucoma, damage to the optic nerve, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, or may result in secondary ocular infections. Viral, bacterial and fungal infections of the cornea may be exacerbated by the application of steroids. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with the use of topical steroids. Acute purulent untreated infection of the eye may be masked or activity enhanced by the presence of steroid medication. • These drugs are not effective in mustard gas keratitis and Sjogren's keratoconjunctivitis. • If irritation persists or develops, the patient should be advised to discontinue use and consult prescribing physician. ■ **PRECAUTIONS:** As fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid applications, fungus invasion must be suspected in any persistent corneal ulceration where a steroid has been used or is in use. • Intraocular pressure should be checked frequently. • These products are sterile when packaged. To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or any other surface with the dropper tip of the bottle. Keep out of the reach of children. Keep bottle tightly closed. Protect from light. STORE AT CONTROLLED ROOM TEMPERATURE (15°-30°C) (59°-86°F). • **Pregnancy: Teratogenic Effects: Pregnancy Category C:** Animal reproductive studies have not been conducted with prednisolone sodium phosphate. It is also not known whether prednisolone sodium phosphate can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Prednisolone sodium phosphate should be given to a pregnant woman only if clearly needed. • The effect of prednisolone sodium phosphate on the later growth, development and functional maturation of the child is unknown. • **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when prednisolone sodium phosphate is administered to a nursing woman. • **Pediatric Use:** Safety and effectiveness in children have not been established. ■ **ADVERSE REACTIONS:** The following adverse reactions have been reported: glaucoma with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infections from pathogens including herpes simplex and fungi, and perforation of the globe. • Rarely, filtering blebs have been reported when topical steroids have been used following cataract surgery. • Rarely, stinging or burning may occur. ■ **DOSAGE AND ADMINISTRATION:** Depending on the severity of inflammation, instill one or two drops of solution into the conjunctival sac up to every hour during the day and every two hours during the night as necessary as initial therapy. • When a favorable response is observed, reduce dosage to one drop every four hours. • Later, further reduction in dosage to one drop three to four times daily may suffice to control symptoms. • The duration of treatment will vary with the type of lesion and may extend from a few days to several weeks, according to therapeutic response. 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[1] *Kupferman, A., Ph.D., and Leibowitz, H.M., M.D. Topically applied steroids in corneal disease. Arch Ophthalmol: 92;1974, 331-334.*

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VOLUME 105

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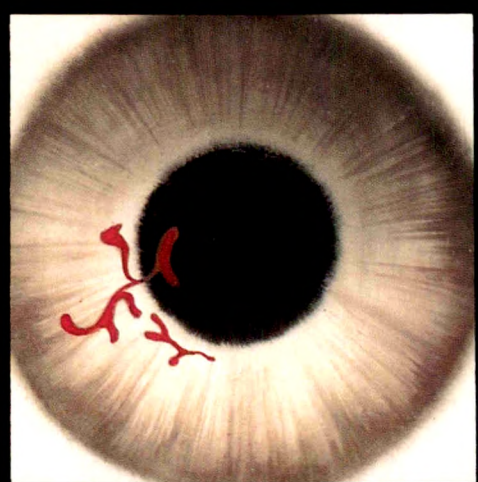
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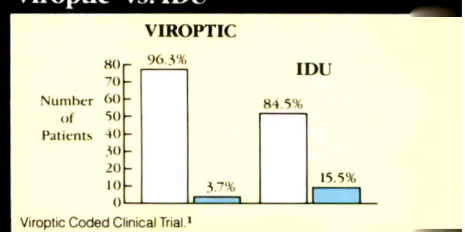
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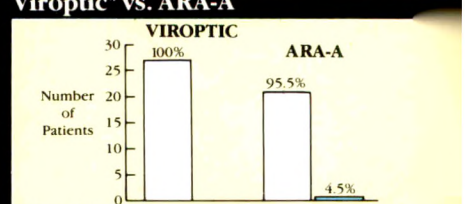
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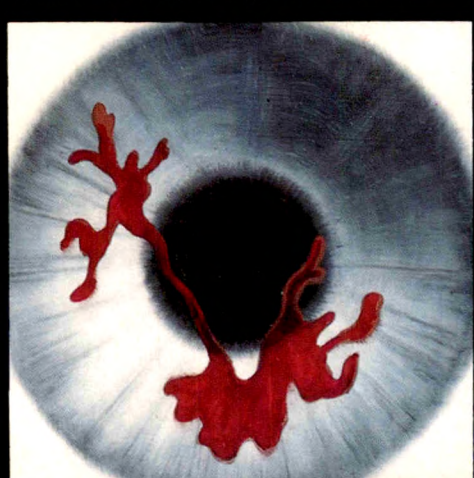
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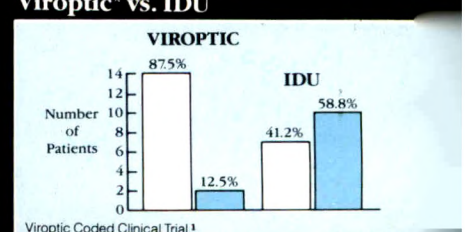
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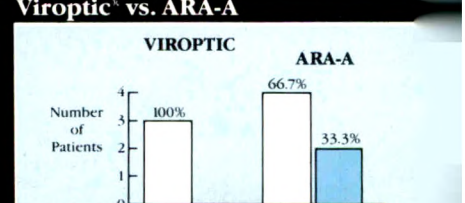
(Medical artist's conception of typical Geographic Lesion)

Viroptic® vs. IDU



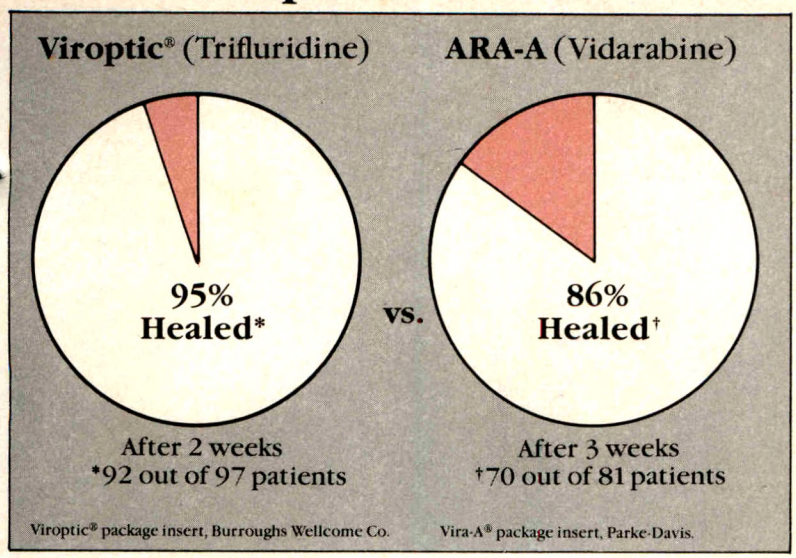
Viroptic Coded Clinical Trial.[1]

Viroptic® vs. ARA-A



Adapted from *Adenine Arabinoside: An Antiviral Agent*, Raven Press, New York, 1975, p 403.[2]

Viroptic® vs ARA-A



Ninety-five percent of patients in Viroptic clinical trials responded within two weeks. By contrast, an examination of controlled trials for ARA-A (vidarabine) reveals that 86% of patients had responded (corneal re-epithelialization had occurred) after three weeks of therapy. So for some patients, treatment with Viroptic may mean relief from suffering and recovery from herpetic keratitis a full week sooner.

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"We do use idoxuridine and vidarabine where acute infections do not respond to trifluridine, but, in my opinion, trifluridine is now the drug of choice for the treatment of superficial herpes, with no exceptions."[3]

References

1. Data on file, Medical Division, Burroughs Wellcome Co.
2. McKinnon JR, McGill JI, Jones BR: A coded clinical evaluation of adenine arabinoside and trifluorothymidine in the treatment of ulcerative herpetic keratitis, in Pavan-Langston D, Buchanan RA, Alford CA Jr (eds): *Adenine Arabinoside: An Antiviral Agent,* Raven Press, New York, 1975, p 403.
3. Kaufman HE, Centifanto-Fitzgerald YM, Varnell ED: Herpes simplex keratitis. *Ophthalmology* 1983;90:700-706.

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CONTRAINDICATIONS: Hypersensitivity or chemical intolerance to trifluridine.

WARNINGS: Do not administer more than nine drops daily. If there is no sign of improvement after seven days or complete re-epithelialization has not occurred after 14 days, other forms of therapy should be considered. Avoid administering VIROPTIC continuously for longer than 21 days.

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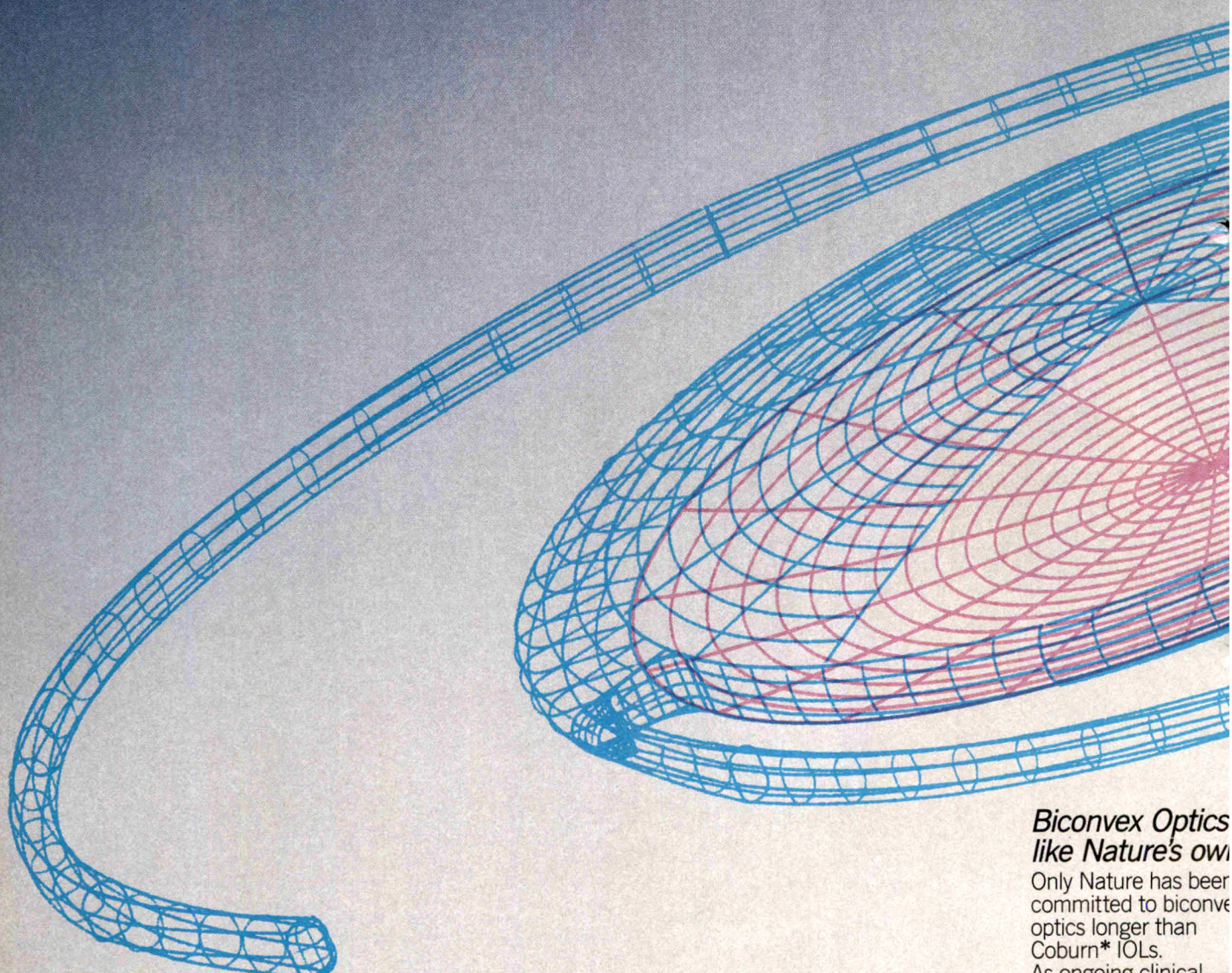
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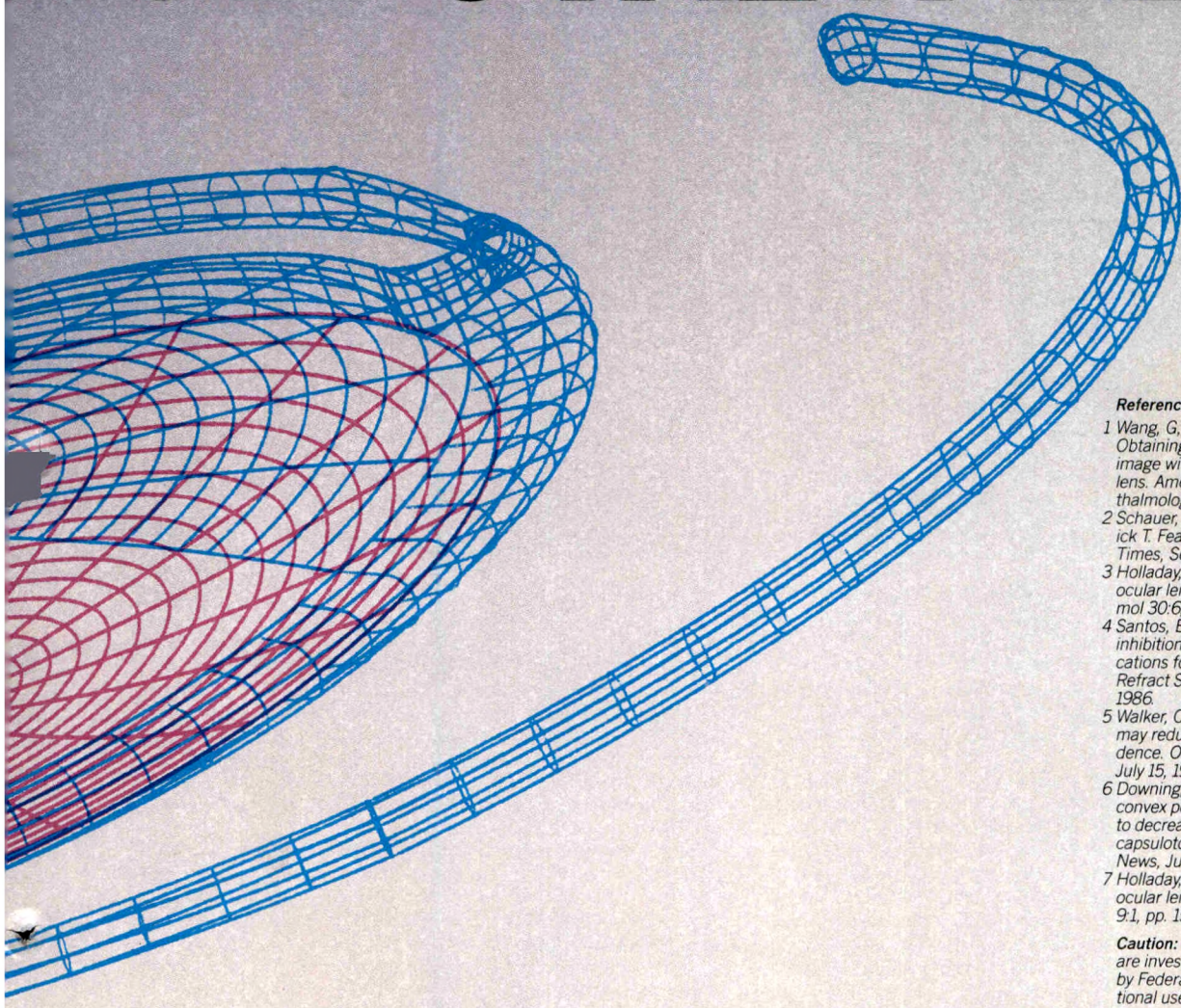
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References:

1 Wang, G, and Pomerantzeff, O: Obtaining a high-quality retinal image with a biconvex intraocular lens. American Journal of Ophthalmology 94:87-90, 1982.

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7 Holladay, JT, et al: The ideal intraocular lens. The CLAO Journal, 9:1, pp. 15-19, January, 1983.

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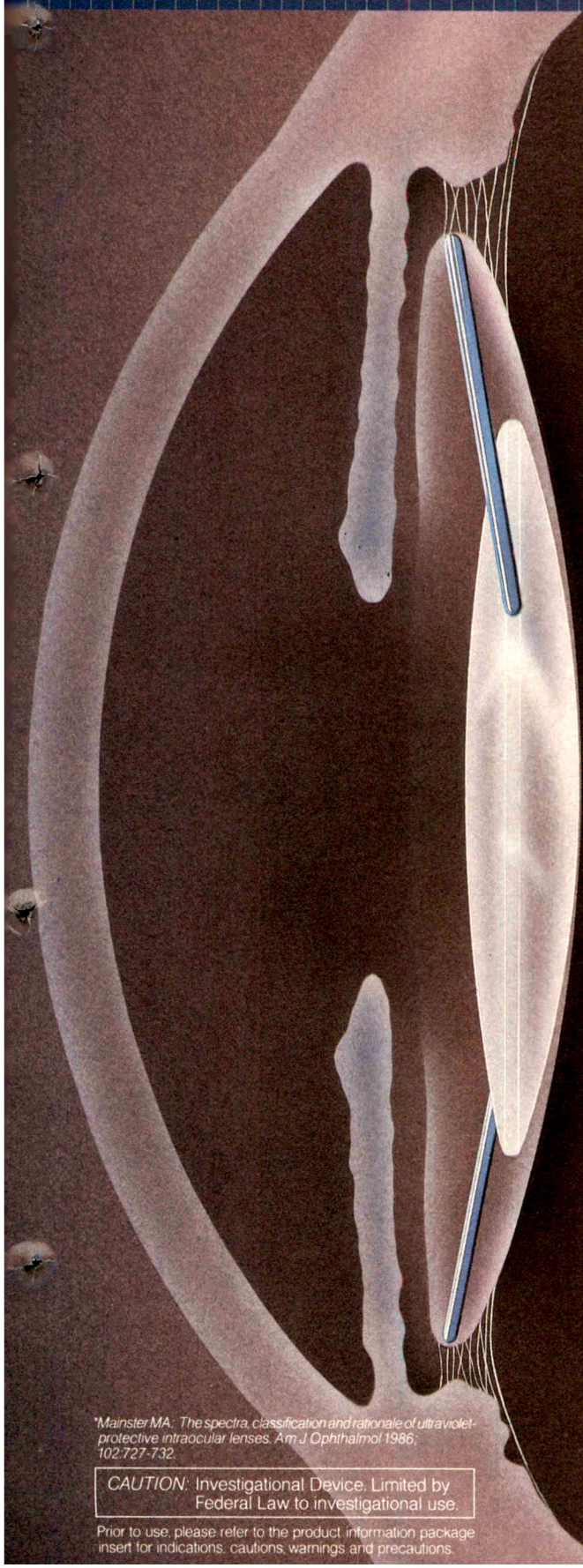
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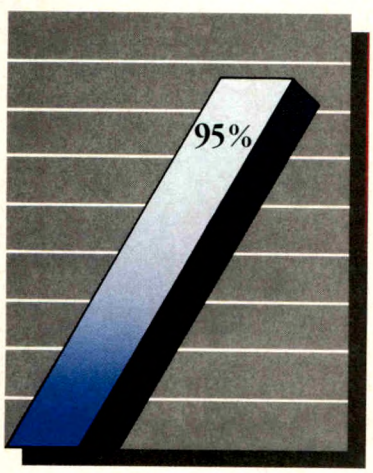
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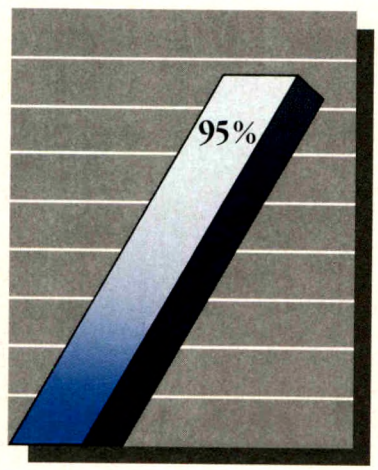
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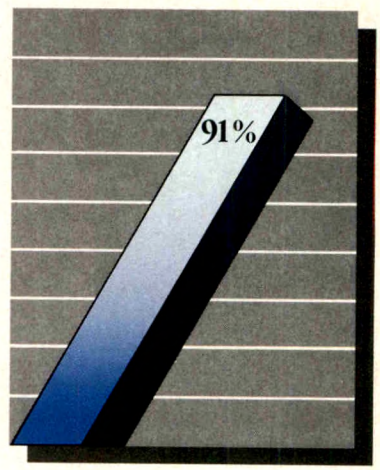
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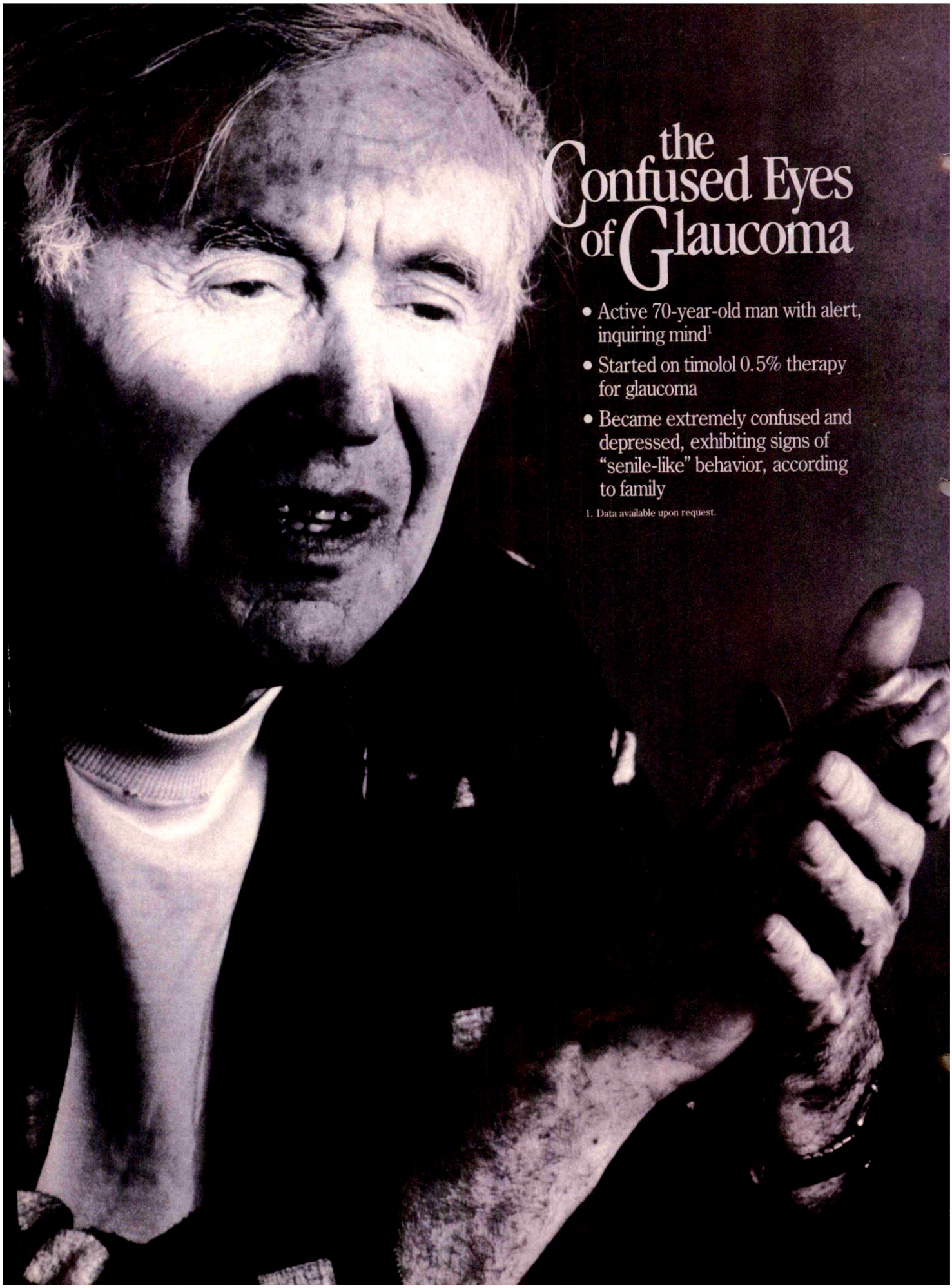
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PRECAUTIONS: Patients who are receiving a beta-adrenergic blocking agent orally and BETOPTIC Ophthalmic Solution should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

While BETOPTIC Ophthalmic Solution has demonstrated a low potential for systemic effect, it should be used with caution in patients with diabetes (especially labile diabetes) because of possible masking of signs and symptoms of acute hypoglycemia. Beta-adrenergic blocking agents may mask certain signs and symptoms of hyperthyroidism and their abrupt withdrawal might precipitate a thyroid storm.

Consideration should be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anesthesia because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli.

Pulmonary: BETOPTIC Ophthalmic Solution, a cardioselective beta-blocker, has produced only minimal effects in patients with reactive airway disease; however, caution should be exercised in the treatment of patients with excessive restriction of pulmonary function.

Drug Interactions: Although BETOPTIC Ophthalmic Solution used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with BETOPTIC Ophthalmic Solution and epinephrine has been reported occasionally.

Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia. Caution should be exercised in patients using concomitant adrenergic psychotropic drugs.

Ocular: In patients with angle-closure glaucoma, the immediate treatment objective is to reopen the angle by constriction of the pupil with a miotic agent. Betaxolol has no effect on the pupil; therefore, BETOPTIC Ophthalmic Solution should be used with a miotic to reduce elevated intraocular pressure in angle-closure glaucoma.

As with the use of other antiglaucoma drugs, diminished responsiveness to BETOPTIC Ophthalmic Solution after prolonged therapy has been reported in some patients. However, in one long-term study in which 250 patients have been followed for a mean period of two years, no significant difference in mean intraocular pressure has been observed after initial stabilization.

Pregnancy and Nursing: As with any drug, BETOPTIC Ophthalmic Solution should be used in pregnant or nursing women only when the anticipated benefits outweigh the risks.

Usage in Children: Clinical studies to establish the safety and efficacy in children have not been performed.

ADVERSE REACTIONS:

Ocular: BETOPTIC Ophthalmic Solution has been well tolerated. Discomfort of short duration was experienced by one in four patients, but none discontinued therapy; occasional tearing has been reported. Rare instances of decreased corneal sensitivity, erythema, itching sensation, corneal punctate staining, keratitis, anisocoria and photophobia have been reported.

Systemic: Systemic reactions following topical administration of BETOPTIC Ophthalmic Solution have been reported rarely (e.g., insomnia and depressive neurosis).

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Limited Registration

Location: Museum Boymans-van Beuningen
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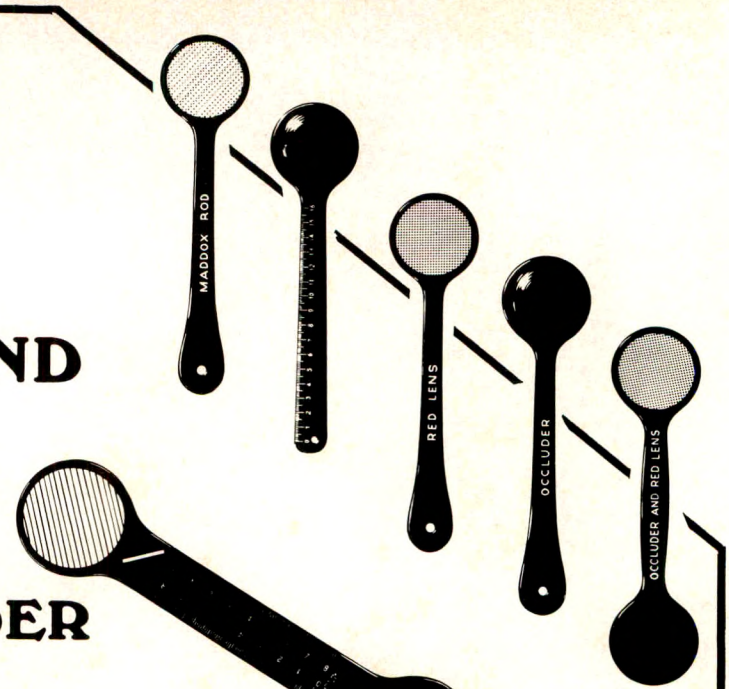
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Registration Fees

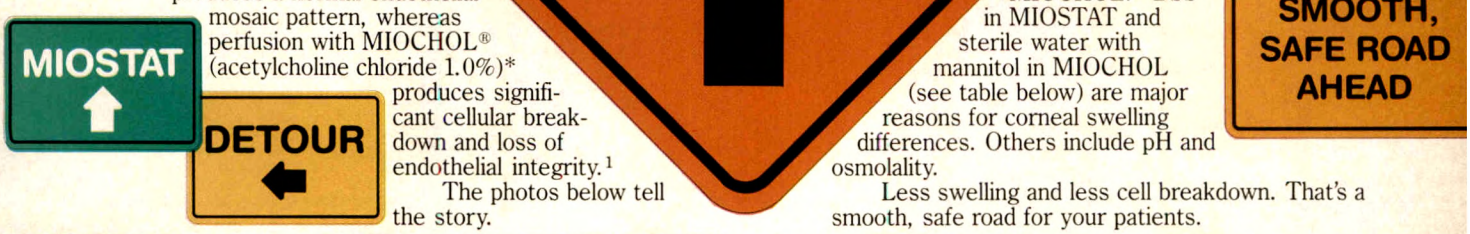
[ ]	Physicians	$150.00
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MIOSTAT®: Less endothelial cell breakdown.

A new study reveals that in-vitro perfusion of *human corneal endothelia* with MIOSTAT® (Carbachol 0.01%) intraocular agent produces a normal endothelial mosaic pattern, whereas perfusion with MIOCHOL® (acetylcholine chloride 1.0%)* produces significant cellular breakdown and loss of endothelial integrity.[1]

The photos below tell the story.



MIOSTAT® (Carbachol 0.01%)
The SEM of human corneal endothelium perfused with BSS PLUS® for one hour, then 15 minutes with 0.01% carbachol chloride followed by BSS PLUS for an additional 1¾ hours. The mosaic pattern of endothelial cells is intact.



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MIOCHOL® (Acetylcholine chloride 1.0%)
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MIOSTAT. The safe road for you and your patient.

1. Yee, R. W., Edelhauser, H. F.: Comparison of intraocular acetylcholine and carbachol. Journal of Cataract Refractive Surgery — Vol 12, January 1986.

**"MIOCHOL" is a trademark of CooperVision Pharmaceuticals, Inc.*

MIOSTAT®: Less corneal swelling.

Corneal thickness measurements taken throughout a three-hour period showed *significantly less corneal swelling* with MIOSTAT than with MIOCHOL.[1] BSS® in MIOSTAT and sterile water with mannitol in MIOCHOL (see table below) are major reasons for corneal swelling differences. Others include pH and osmolality.

Less swelling and less cell breakdown. That's a smooth, safe road for your patients.

Here's safety in chemical composition:

Chemical Comparisons

	MIOCHOL®	*vs MIOSTAT®*
Active ingredient	*1.0% Acetylcholine*	*.01% Carbachol*
Vehicle	*Sterile water*	*BSS® Balanced Salt Solution*
Ions present	*Chloride*	*Sodium, Potassium, Calcium**, Magnesium, Chloride*
Other ingredients	*Mannitol 3.0%*	*Acetate Citrate*
pH	*6.9**	*7.3*
Osmolality	*290 mOsms*	*305 mOsms*

**Only at time of reconstitution; acidifies rapidly.*

***Calcium is essential for maintaining junctional complexes of endothelial cells.*

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MIOSTAT® (Carbachol 0.01%) Intraocular

DESCRIPTION: MIOSTAT® (Carbachol 0.01%) is a sterile balanced salt solution of Carbachol for intraocular injection. The active ingredient is represented by the chemical structure: $[NH_2COOCH_2CH_2N^+(CH_3)_3]Cl^-$ ESTABLISHED NAME: Carbachol CHEMICAL NAME: Ethanaminium, 2-[(aminocarbonyl) oxy]-N,N,N-trimethyl-, chloride. Each ml contains: Active: Carbachol 0.01%. Inactive: Sodium Chloride 0.64%, Potassium Chloride 0.075%, Calcium Chloride Dihydrate 0.048%, Magnesium Chloride Hexahydrate 0.03%, Sodium Acetate Trihydrate 0.39%, Sodium Citrate Dihydrate 0.17%, Sodium Hydroxide and/or Hydrochloric Acid (to adjust pH) and Water For Injection USP. CLINICAL PHARMACOLOGY: Carbachol is a potent cholinergic (parasympathomimetic) agent with miotic activity. INDICATIONS AND USAGE: Intraocular use for miosis during surgery. CONTRAINDICATIONS: Should not be used in those persons showing hypersensitivity to any of the components of this preparation. WARNINGS: For single-dose intraocular use only. Discard unused portion. Intraocular Carbachol 0.01% should be used with caution in patients with acute cardiac failure, bronchial asthma, peptic ulcer, hyperthyroidism, G.I. spasm, urinary tract obstruction and Parkinson's disease. ADVERSE REACTIONS: Side effects such as flushing, sweating, epigastric distress, abdominal cramps, tightness in urinary bladder, and headache have been reported after systemic or topical use of carbachol. These symptoms were not reported following intraocular use of carbachol 0.01% in pre-marketing studies. Corneal clouding, persistent bullous keratopathy and post-operative iritis following cataract extraction with utilization of intraocular carbachol have been reported in an occasional patient. As with all miotics, retinal detachment has been reported when miotics are used in certain susceptible individuals. OVERDOSAGE: Atropine should be administered parenterally (for dosage refer to Goodman & Gilman or other pharmacology reference). DOSAGE AND ADMINISTRATION: Aseptically remove the sterile vial from the blister package by peeling the backing paper and dropping the vial onto a sterile tray. Withdraw the contents into a dry sterile syringe, and replace the needle with an atraumatic cannula prior to intraocular irrigation. *No more than one-half milliliter* should be gently instilled into the anterior chamber for the production of satisfactory miosis. It may be instilled before or after securing sutures. Miosis is usually maximal within two to five minutes after application. HOW SUPPLIED: In 1.5 ml sterile glass vials packaged twelve to a carton. NDC 0065-0023-15.

Mr. Jack Marshall • Alcon Surgical • P.O. Box 6600 • Fort Worth, TX 76115-9952

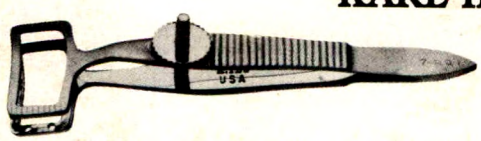
☐ Yes, I'd like to sample Alcon's MIOSTAT® intraocular agent.
☐ I'd like a copy of the Yee/Edelhauser study.

Approximate number of cataract surgeries per month (circle one):
0-5 6-10 11-20 21-49 50+

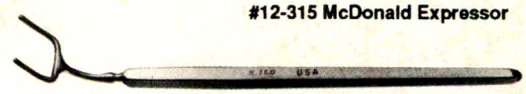
I use an intraocular miotic agent in ____% of cataract cases.

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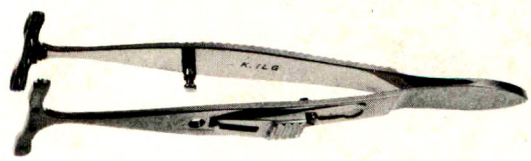
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irrigating, with a tear-drop shaped point on tip





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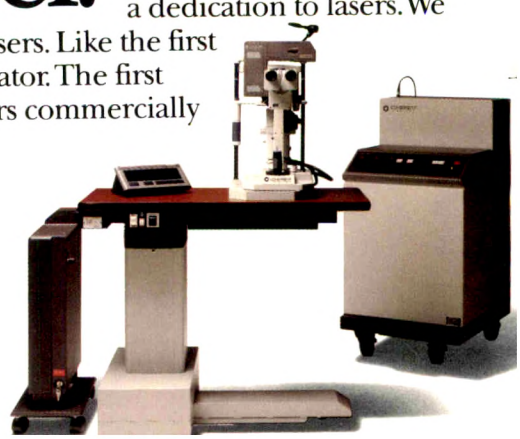
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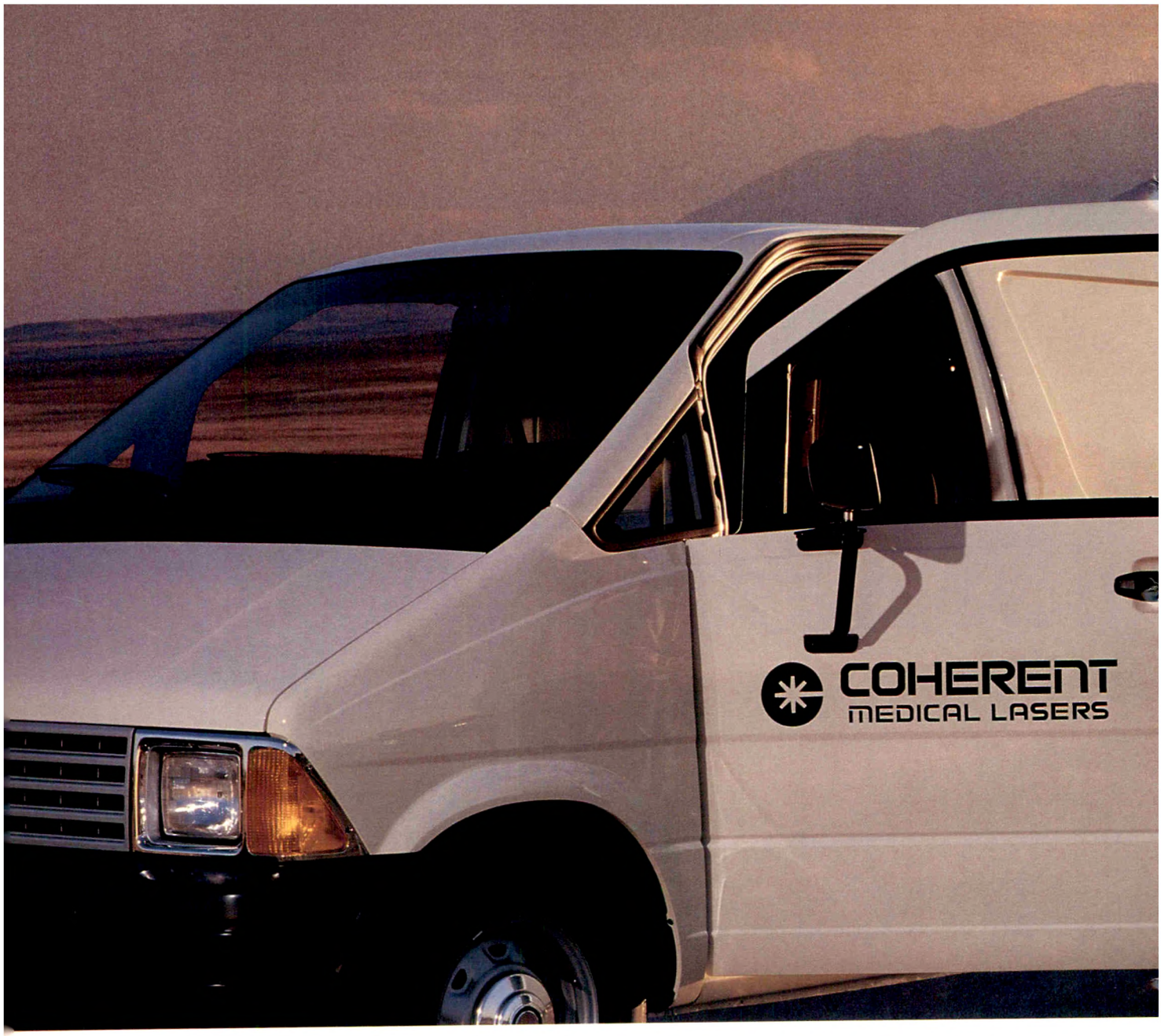
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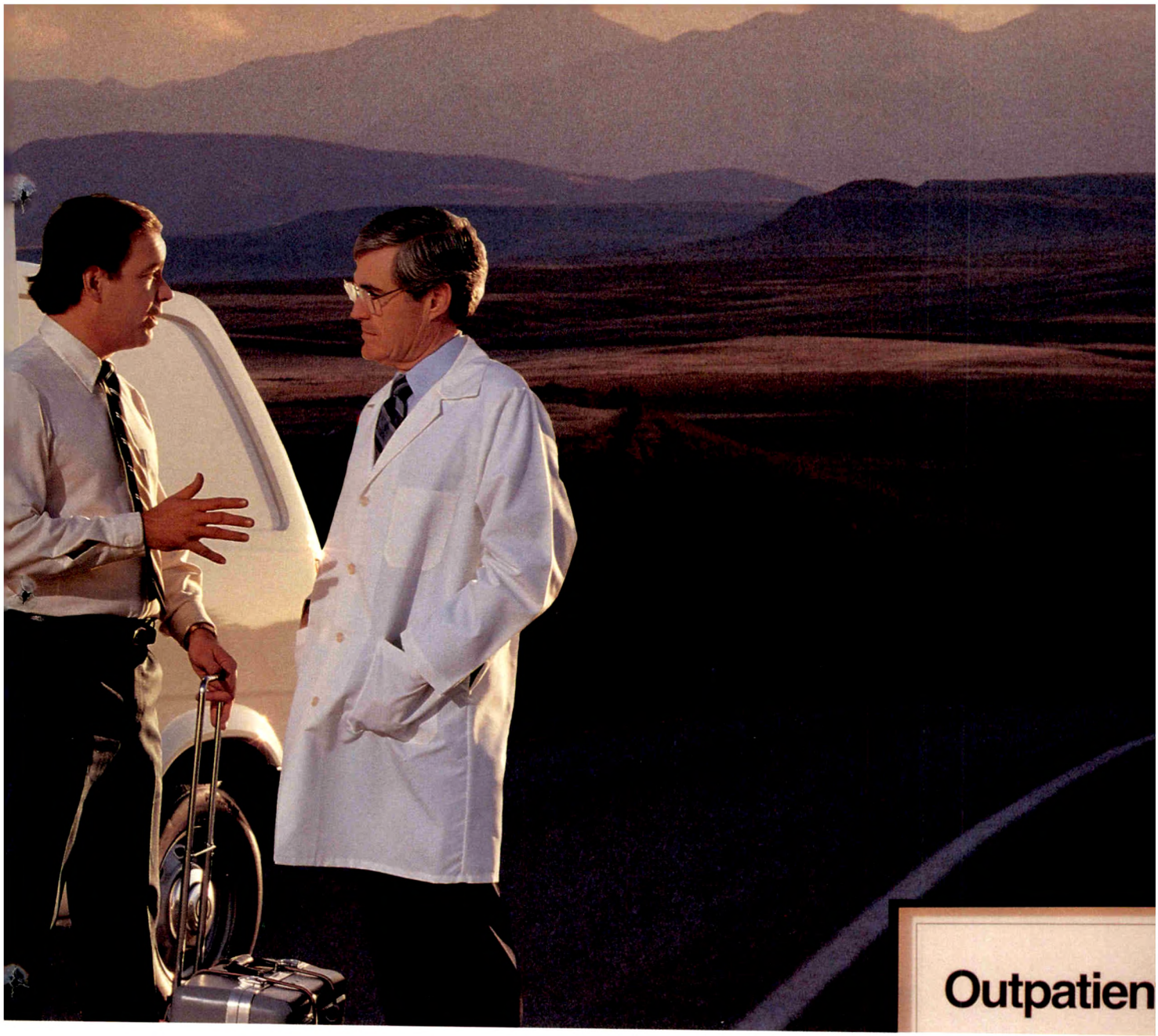
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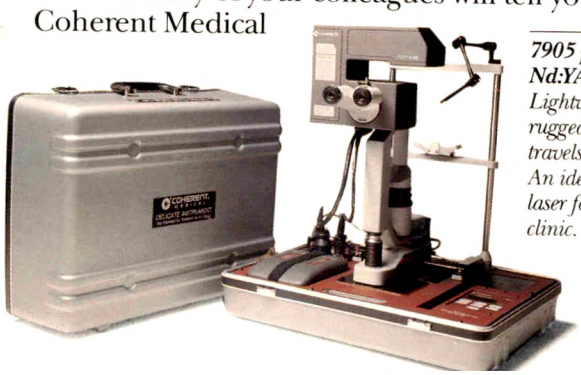


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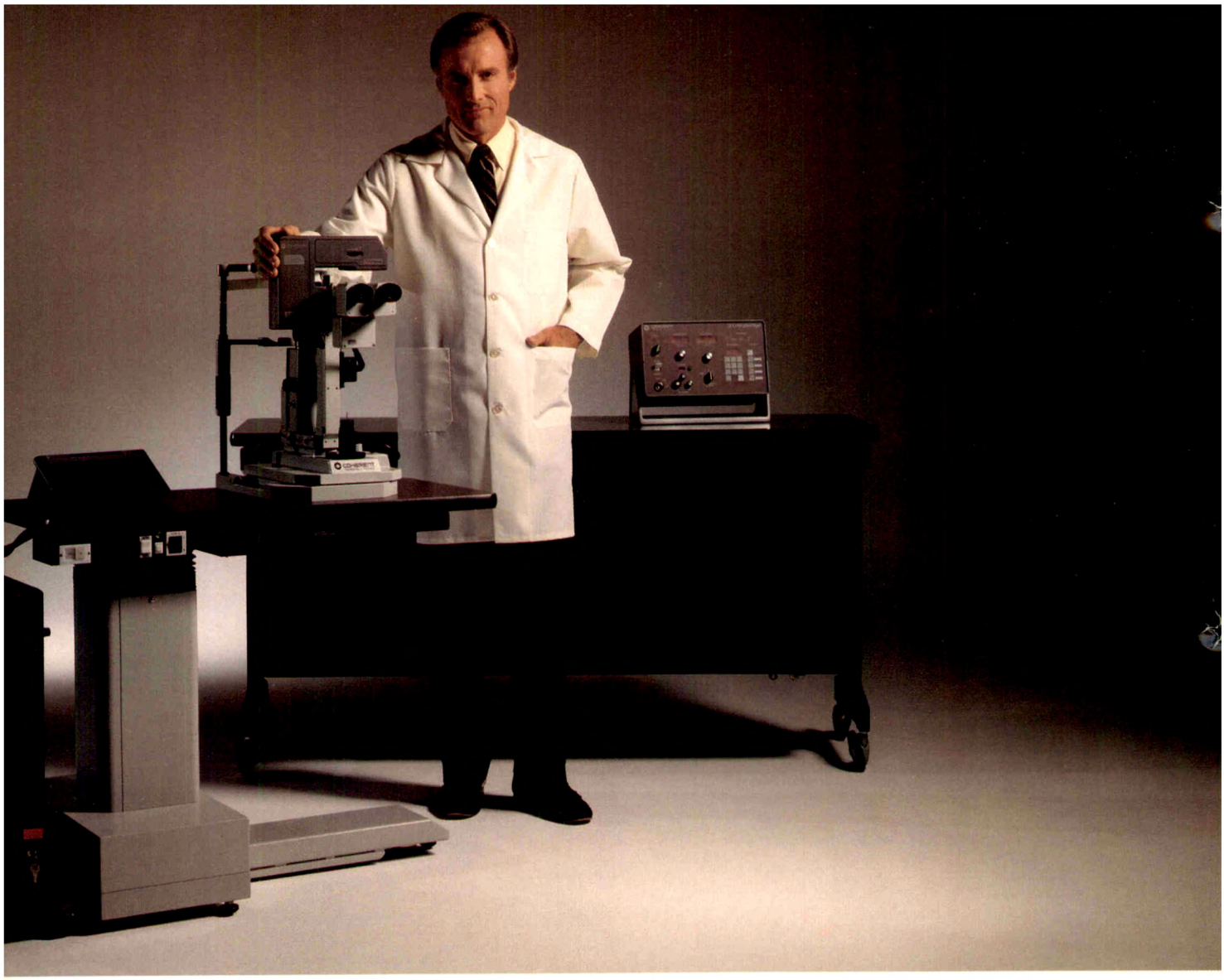
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AKORN HEALS MARKET WOUNDS

THE AKORN STREET JOURNAL.

VOL. LXXX NO. 11 ★★ National Edition FRIDAY JANUARY 1, 1988 Abita Springs, La. 50 CENT

Akorn Helps Doctors Recoup Losses

The smart money among the M.D.'s is moving to Akorn. It is no insider's secret that the quality line of Akorn ophthalmic products has produced more profits for less investment for ophthalmologists than any of Akorn's competitors. No minimum orders are required by Akorn and the company offers the best goods return policy available in the ophthalmic industry. The past year's sales reflect the interest shown by the profession.

"By holding the price line Akorn made it easy for their customers to make a profit without sacrificing quality during ...ent bear market," said Barry ...any's president.

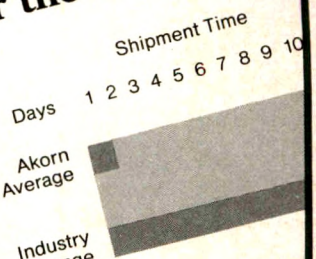
What's News

* * *

Looking forward to 1988, Akorn has again expanded its line of products. Making their debut in the Akorn line are solar shields, surgical drape supports, pen lights and lid scrub. These new additions to the Akorn line of ophthalmic products have increased the selection to over one hundred quality products. Each Akorn product meets the exacting standards that are required by the profession. The value provided by Akorn is present in all of the new product additions, dependable therapy, top quality and immediate delivery.

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Imaging of Cerebral Blood Flow and Metabolism in Amblyopia by Positron Emission Tomography

Joseph L. Demer, M.D., Gunter K. von Noorden, M.D., Nora D. Volkow, M.D., and K. Lance Gould, M.D.

We used positron emission tomography to study monocular visual activation of various brain regions in four amblyopic and two normally sighted adults. Imaging of relative cerebral blood flow using the tracer $H_2{}^{15}O$ showed reduced activation of primary visual cortex by the amblyopic as compared with the sound eye. Imaging of relative cerebral glucose metabolism using the tracer [^{18}F]-2-deoxyglucose showed equal activation of primary visual cortex by either eye in the control subject, but reduced activation of primary and accessory visual cortex by the amblyopic as compared with the sound eye in two amblyopic subjects. Relative glucose metabolism was consistently higher in the frontal and temporal lobes contralateral to the viewing eye, both in normal and amblyopic subjects.

© American Journal of Ophthalmology 105:337–347, April, 1988

Penetrating Keratoplasty for Pseudophakic Bullous Keratopathy After Extracapsular Cataract Extraction

Steven B. Koenig, M.D., and Richard O. Schultz, M.D.

Seventeen women underwent simple penetrating keratoplasty for pseudophakic bullous keratopathy after extracapsular cataract extraction. Corneal edema occurred an average of eight months after cataract surgery (range, zero to 32 months). Of 17 corneal grafts, 16 (94%) have remained clear during an average follow-up period of 14 months (range, two to 32 months). One eye had a non-immunologic graft failure. Of 16 eyes with clear grafts, 14 (87%) achieved a visual acuity of 20/40 or better after surgery. Two eyes with a visual acuity of 20/50 and 20/200 had opacified posterior capsules and one demonstrated age-related macular degeneration. One eye with a postoperative visual acuity of 20/40 demonstrated cystoid macular edema. Fifteen of 17 contralateral eyes showed slit-lamp evidence of endothelial dystrophy.

© American Journal of Ophthalmology 105:348–353, April, 1988

The Surgical Management of Overcorrection in Myopic Epikeratophakia

Bruce D. Nichols, M.D., F.R.C.S.(C.), Richard L. Lindstrom, M.D., and Alan V. Spigelman, M.D.

Three patients underwent myopic epikeratophakia that resulted in overcorrection. The surgical management of these cases involved resuturing the myopic lenticule to flatten the peripheral curvature and reduce the amount of minus power. A reduction in the overcorrection was achieved in all cases.

© American Journal of Ophthalmology 105:354–356, April, 1988

The Risk of Cytomegalovirus Transmission by Penetrating Keratoplasty

Edward J. Holland, M.D., Steven R. Bennett, M.D., Rochelle Brannian, R.N., James C. Osborne, M.D., James A. Goeken, M.D., and Jay H. Krachmer, M.D.

To investigate the risk of cytomegalovirus transmission by corneal transplantation, we quantitated anticytomegalovirus IgG levels of donor, preoperative, and postoperative serum samples. Of 118 patients, 79 (67%) were seropositive preoperatively. Twenty-five patients who were seronegative preoperatively received a graft from a positive donor and two (8%) seroconverted. Eleven patients who were seronegative preoperatively received a graft from a negative donor and one (9%) seroconverted. None of the patients who seroconverted had a febrile illness and all three grafts were clear.

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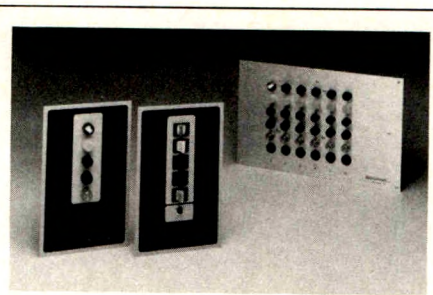
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Microbial Keratitis Associated With Contaminated Ocular Medications

Oliver D. Schein, M.D., Paul J. Wasson, M.D., S. Arthur Boruchoff, M.D., and Kenneth R. Kenyon, M.D.

We studied seven cases of severe gram-negative microbial keratitis associated with the use of contaminated topical ocular medications. Five cases involved *Pseudomonas aeruginosa*, one involved *Serratia marcescens*, and one involved *Proteus mirabilis*. In each case the same organism was cultured from corneal scrapings and from the medication. Either prednisolone acetate (one case) or timolol maleate (seven cases) was implicated in all instances.

© American Journal of Ophthalmology 105:361–365, April, 1988

Ocular Involvement in Mycotic Sinusitis Caused by *Bipolaris*

Walter M. Jay, M.D., Robert W. Bradsher, M.D., Brad LeMay, M.D., Nancy Snyderman, M.D., and Edgardo J. Angtuaco, M.D.

We examined two patients with unilateral ophthalmologic findings secondary to pansinusitis caused by *Bipolaris*. Both patients were healthy young men. One patient had a gradual visual loss, whereas the other showed proptosis. Surgical debridement was the primary treatment in both patients. One patient received antifungal therapy, whereas the other was cured with surgery alone.

© American Journal of Ophthalmology 105:366–370, April, 1988

Vitrectomy for Impending Idiopathic Macular Holes

William E. Smiddy, M.D., Ronald G. Michels, M.D., Bert M. Glaser, M.D., and Serge de Bustros, M.D.

We performed pars plana vitrectomy in 15 patients with physical changes and visual loss believed to indicate impending macular hole formation. Twelve (80%) of 15 eyes have not progressed to macular holes during a minimum follow-up period of 15 months (average, 26 months). In these 12 patients final vision was within one line of the preoperative vision in four eyes, improved two or more lines in five eyes, and was two lines worse in three eyes. Decreased vision in all three eyes was the result of progressive lenticular nuclear sclerosis. A thin sheet of cortical vitreous fibers was sometimes found intraoperatively on the surface of the retina, despite an apparent complete posterior vitreous detachment.

© American Journal of Ophthalmology 105:371–376, April, 1988

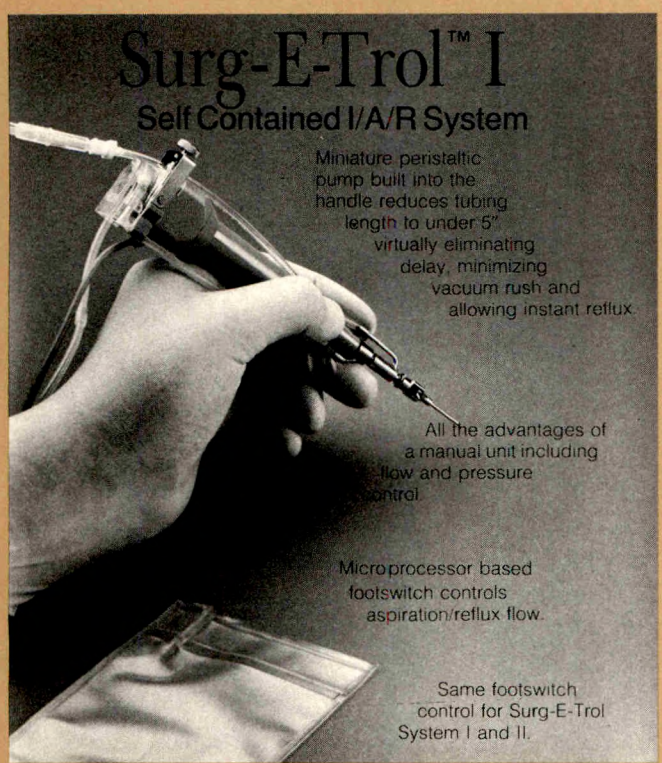
Peripheral Retinal Cryopexy for Subtotal Vitreous Hemorrhage

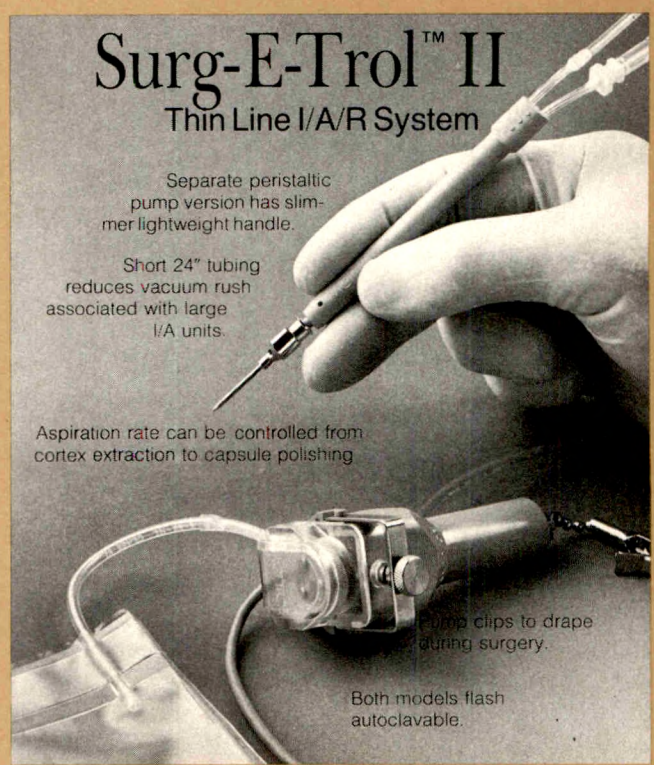
William H. Ross, M.D., and Michael J. Gottner, M.D.

We used peripheral retinal cryopexy to treat 20 eyes in 15 patients with subtotal vitreous hemorrhage secondary to proliferative diabetic retinopathy. In 18 eyes, complete panretinal photocoagulation had been performed before the subtotal vitreous hemorrhage and the subsequent cryopexy. The length of follow-up averaged 16 months. The vitreous hemorrhage completely cleared in 11 eyes (55%) and partially cleared in six eyes (30%). Visual acuity after treatment improved in 13 eyes (65%), remained unchanged in six eyes (30%), and decreased in one eye (5%).

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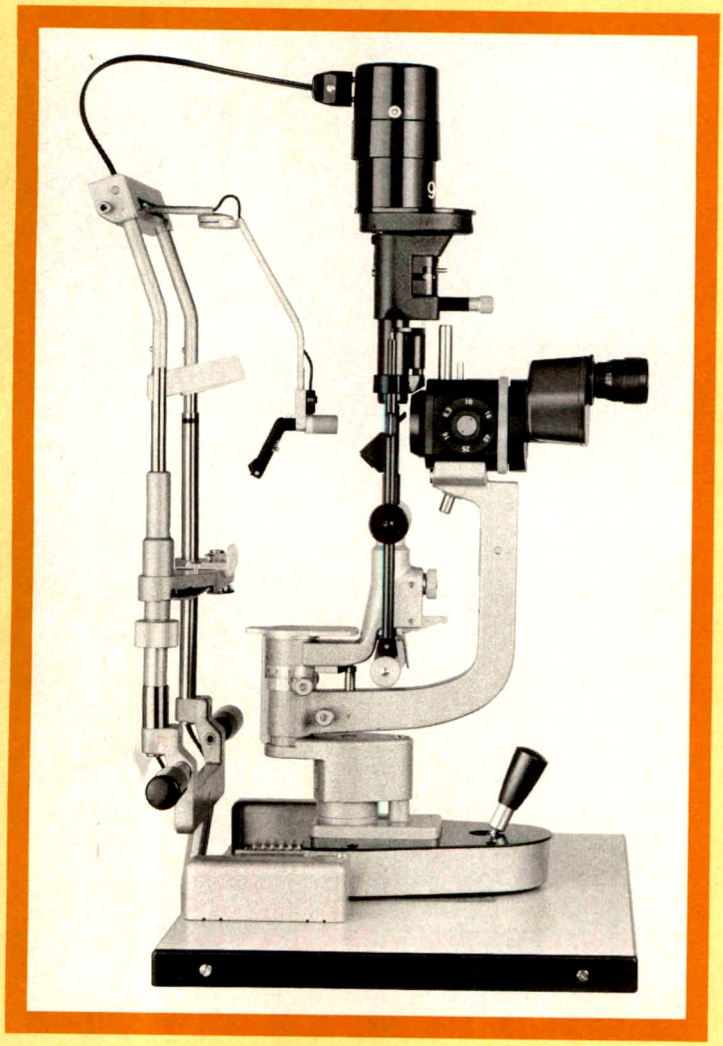
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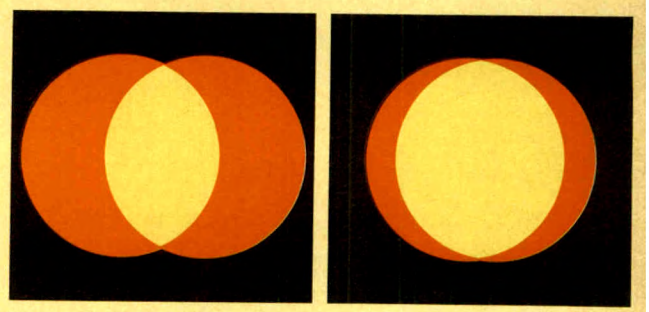
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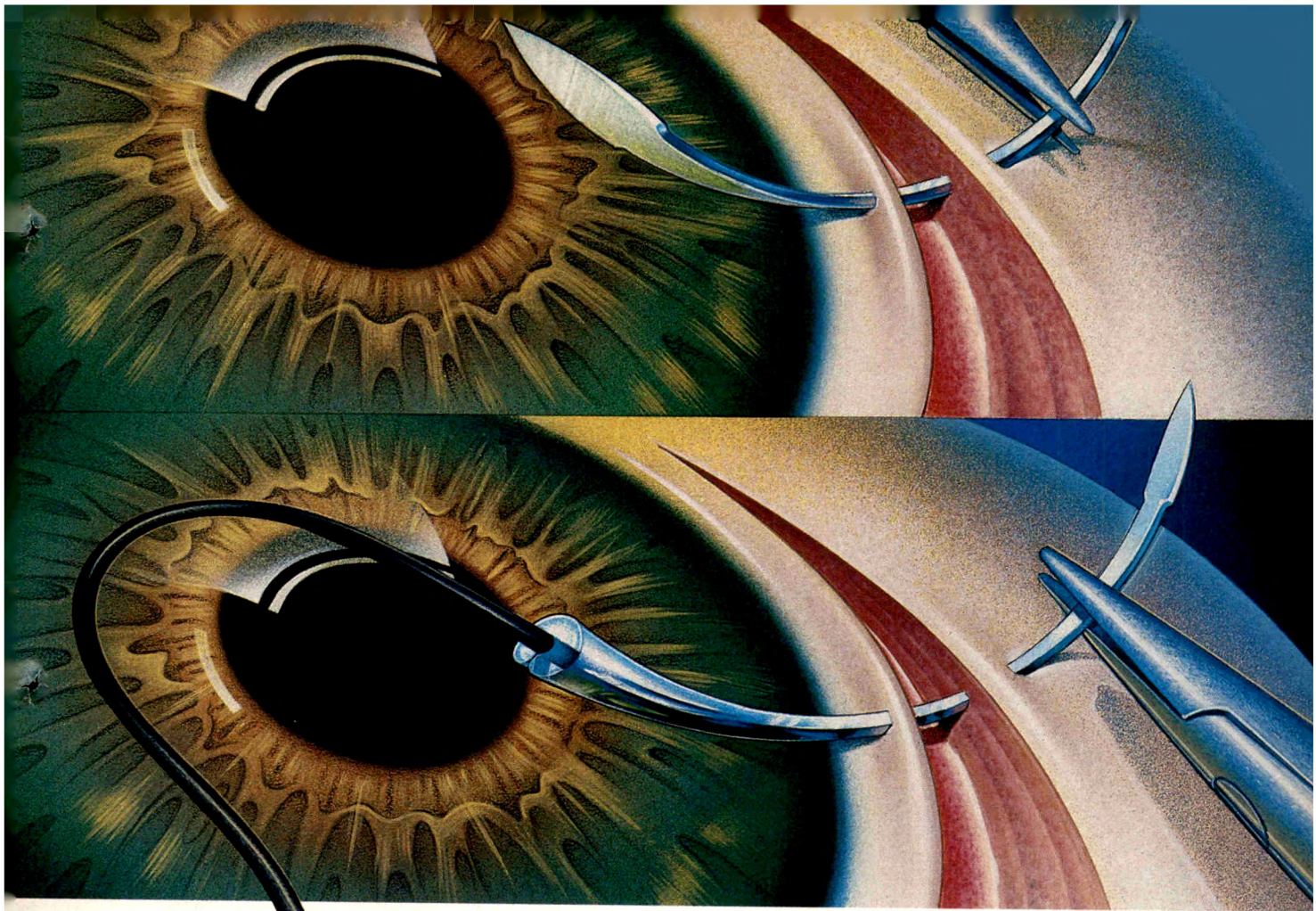
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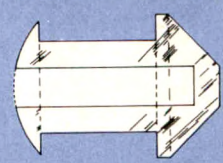
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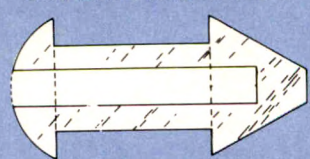
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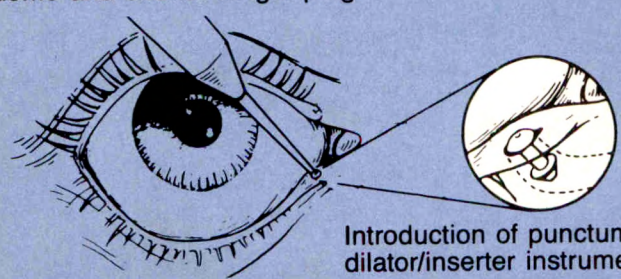
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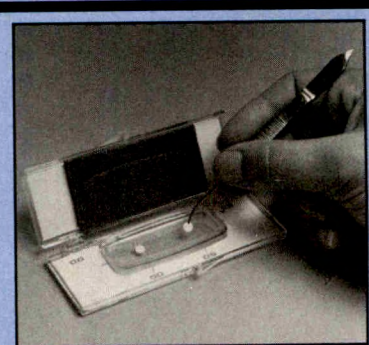
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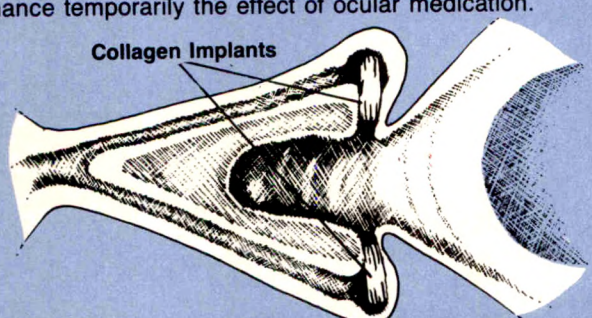
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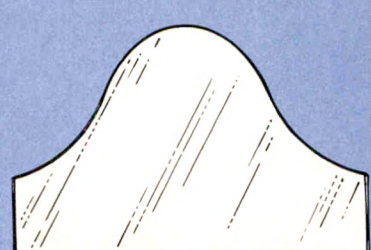
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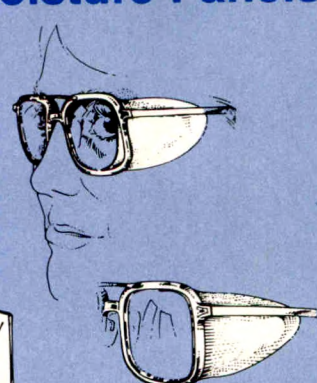
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Immunohistopathologic Findings in Proliferative Diabetic Retinopathy

Christophe Baudouin, M.D., Danielle Fredj-Reygrobellet, Ph.D., Philippe Lapalus, Ph.D., and Pierre Gastaud, Ph.D.

We performed immunopathologic studies on pars plana specimens obtained by biopsy in patients with diabetes mellitus type I or II and by autopsy in diabetic patients and normal subjects. Frozen sections were treated with several antisera, including anti-IgG, complement components, and major histocompatibility complex antigens, as well as anti-factor VIII to detect vascular structures. The results showed IgG in a linear pattern at the basal pole of pigment epithelial cells and complement deposits of C3c, C3d, and C4 at the same location and in the stroma. HLA-DR expression was found at the level of the pigmented cells. These data suggest that some autoimmune processes may be involved in proliferative diabetic retinopathy at the level of the pigment epithelium, but it is unknown whether they are an epiphenomenon of neovascularization or if they play a role in its initiation.

© American Journal of Ophthalmology 105:383–388, April, 1988

Infantile Glaucoma in Down's Syndrome (Trisomy 21)

Elias I. Traboulsi, M.D., Elliot Levine, M.D., Marilyn B. Mets, M.D., Edward S. Parelhoff, M.D., John F. O'Neill, M.D., and Douglas E. Gaasterland, M.D.

We examined five patients with Down's syndrome and bilateral infantile glaucoma. In the first few months of life four patients had large cloudy corneas, breaks in Descemet's membrane, increased intraocular pressure, photophobia, and tearing. In one patient the diagnosis was delayed until 3½ years of age because of concomitant nasolacrimal duct obstruction. Two patients developed cataracts and retinal detachment and have undergone multiple surgical procedures. The clinical course in these two older patients suggests that coexistence of congenital glaucoma, severe myopia, and cataracts in patients with trisomy 21 strongly predisposes for the development of retinal detachment and poor visual outcome.

© American Journal of Ophthalmology 105:389–394, April, 1988

Effects of Argon Laser Iridotomy on the Corneal Endothelium

William C. Panek, M.D., David A. Lee, M.D., and Robert E. Christensen, M.D.

We studied 14 eyes of 14 patients undergoing argon laser peripheral iridotomy for occludable (narrow) anterior chamber angles. Preoperative and postoperative pachymetry and corneal endothelial cell counts by specular microscopy were obtained centrally and in both the treated and nontreated superior quadrants. No significant differences were found between preoperative and postoperative measurements of corneal thickness and endothelial cell counts in any area.

© American Journal of Ophthalmology 105:395–397, April, 1988

Ferrous Intraocular Foreign Bodies and Magnetic Resonance Imaging

Syd Williams, M.D., Devron H. Char, M.D., William P. Dillon, M.D., Nora Lincoff, and Michael Moseley, Ph.D.

We placed various sized ferrous foreign bodies in and around the eye, sclera, and orbit in a rabbit model before performing magnetic resonance imaging studies. All foreign bodies were detected on plain x-rays. Only one of the largest fragments (3 × 1 × 1 mm) demonstrated movement on exposure to the magnetic field.

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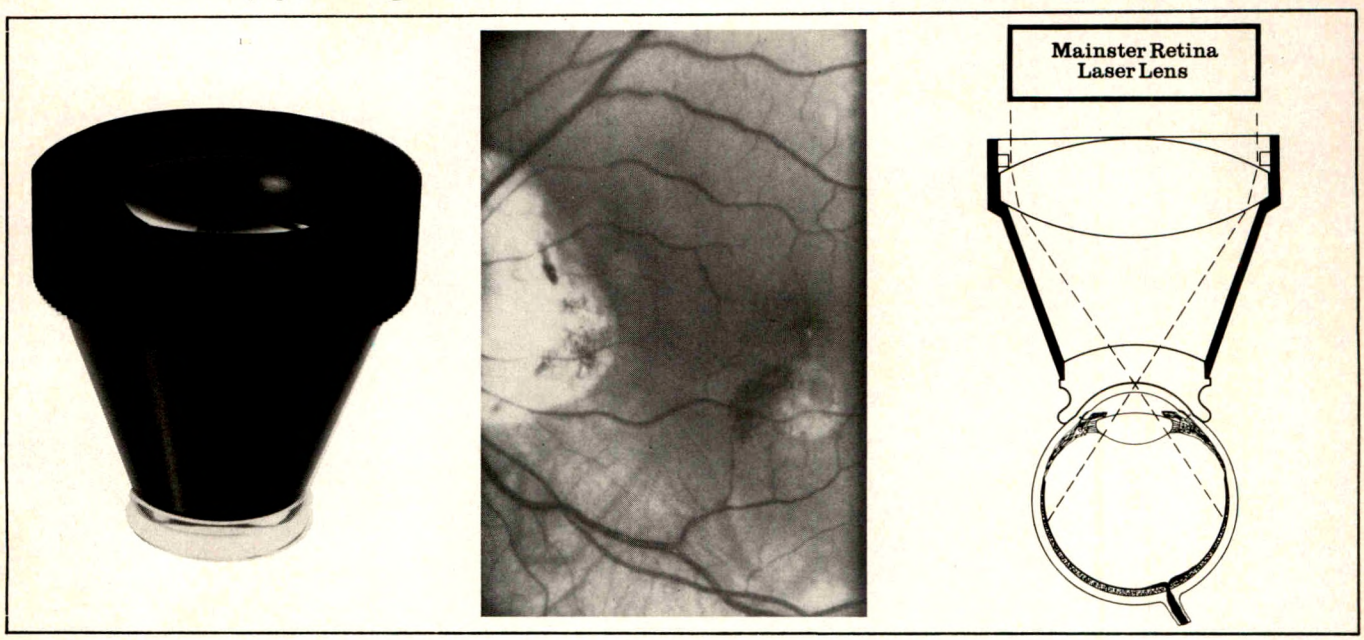


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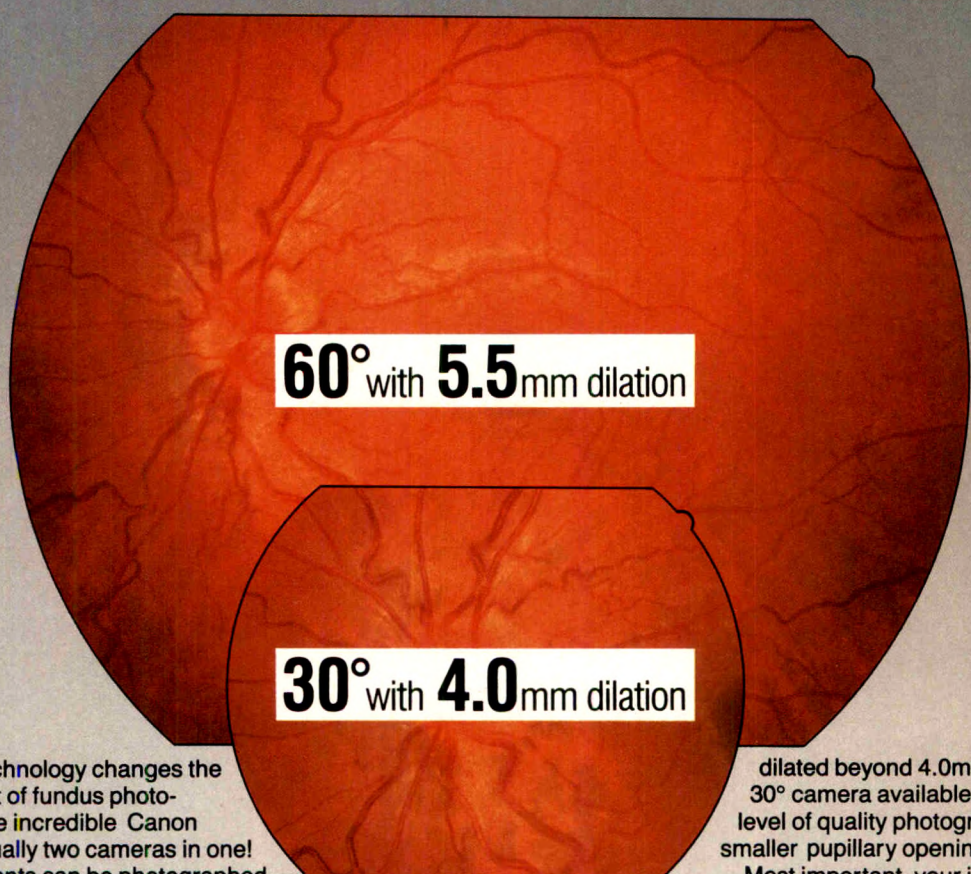
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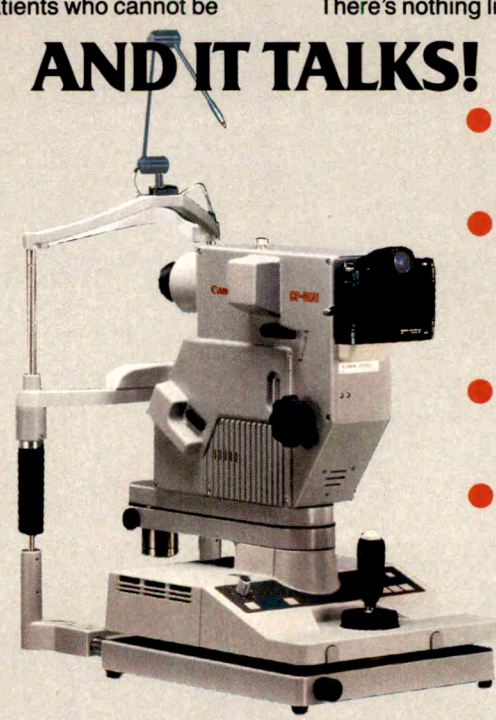
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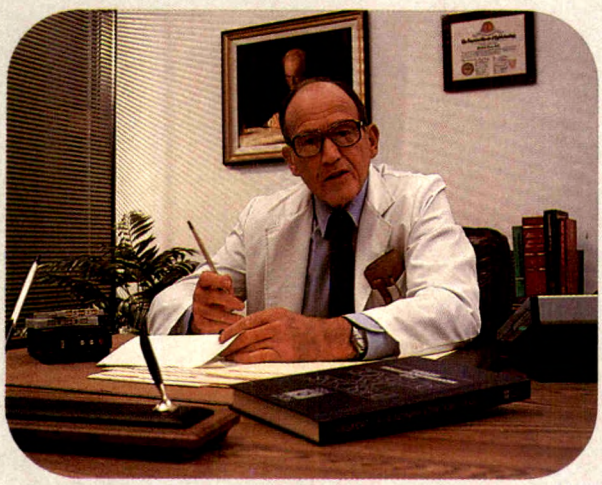
Liquifilm® sterile ophthalmic solution

INDICATIONS AND USAGE: BETAGAN Liquifilm sterile ophthalmic solution has been shown to be effective in lowering intraocular pressure and may be used in patients with chronic open-angle glaucoma or ocular hypertension. **CONTRAINDICATIONS:** BETAGAN is contraindicated in those individuals with bronchial asthma or with a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second and third degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; or hypersensitivity to any component of this product. **WARNINGS:** As with other topically applied ophthalmic drugs, BETAGAN may be absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported with topical application of beta-adrenergic blocking agents (see CONTRAINDICATIONS). **Cardiac Failure:** Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. **In Patients Without a History of Cardiac Failure:** Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, BETAGAN should be discontinued. **Non-allergic Bronchospasm:** In patients with non-allergic bronchospasm or with a history of non-allergic bronchospasm (e.g., chronic bronchitis, emphysema), BETAGAN should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of $beta_2$ receptors. **Major Surgery:** The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. For these reasons, in patients undergoing elective surgery, gradual withdrawal of beta-adrenergic receptor blocking agents may be appropriate. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol (See OVERDOSAGE). **Diabetes Mellitus:** Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia. **Thyrotoxicosis:** Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm. Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people. **PRECAUTIONS: General:** BETAGAN should be used with caution in patients with known hypersensitivity to other beta-adrenoceptor blocking agents. Use with caution in patients with known diminished pulmonary function. In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. BETAGAN has little or no effect on the pupil. When BETAGAN is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone. **Muscle Weakness:** Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalized weakness). **Drug Interactions:** BETAGAN should be used with caution in patients who are receiving a beta-adrenergic blocking agent orally, because of the potential for additive effects on systemic beta-blockade. Although BETAGAN used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with BETAGAN and epinephrine may occur. Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension. **Animal Studies:** No adverse ocular effects were observed in rabbits administered BETAGAN topically in studies lasting one year in concentrations up to 10 times the human dose concentration. **Carcinogenesis, mutagenesis, impairment of fertility:** In a lifetime oral study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign leiomyomas in female mice at 200 mg/kg/day (14,000 times the recommended human dose for glaucoma), but not at 12 or 50 mg/kg/day (850 and 3,500 times the human dose). In a two-year oral study of levobunolol HCl in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of benign hepatomas in male rats administered 12,800 times the recommended human dose for glaucoma. Similar differences were not observed in rats administered oral doses equivalent to 350 times to 2,000 times the recommended human dose for glaucoma. Levobunolol did not show evidence of mutagenic activity in a battery of microbiological and mammalian *in vitro* and *in vivo* assays. Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 1,800 times the recommended human dose for glaucoma. **Pregnancy Category C:** Fetotoxicity (as evidenced by a greater number of resorption sites) has been observed in rabbits when doses of levobunolol HCl equivalent to 200 and 700 times the recommended dose for the treatment of glaucoma were given. No fetotoxic effects have been observed in similar studies with rats at up to 1,800 times the human dose for glaucoma. Teratogenic studies with levobunolol in rats at doses up to 25 mg/kg/day (1,800 times the recommended human dose for glaucoma) showed no evidence of fetal malformations. There were no adverse effects on postnatal development of offspring. It appears when results from studies using rats and studies with other beta-adrenergic blockers are examined, that the rabbit may be a particularly sensitive species. There are no adequate and well-controlled studies in pregnant women. BETAGAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Systemic beta-blockers and topical timolol maleate are known to be excreted in human milk. Caution should be exercised when BETAGAN is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children have not been established. **ADVERSE REACTIONS:** In clinical trials the use of BETAGAN has been associated with transient ocular burning and stinging in about 1 in 4 patients, and with blepharoconjunctivitis in about 1 in 20 patients. Decreases in heart rate and blood pressure have been reported occasionally (see CONTRAINDICATIONS and WARNINGS). The following adverse effects have been reported rarely with the use of BETAGAN: iridocyclitis, headache, transient ataxia, dizziness, lethargy, urticaria and pruritus. Decreased corneal sensitivity has been noted in a small number of patients. Although levobunolol has minimal membrane-stabilizing activity, there remains a possibility of decreased corneal sensitivity after prolonged use. The following additional adverse reactions have been reported with ophthalmic use of $beta_1$ and $beta_2$ (non-selective) adrenergic receptor blocking agents: BODY AS A WHOLE: Headache. CARDIOVASCULAR: Arrhythmia, syncope, heart block, cerebral vascular accident, cerebral ischemia, congestive heart failure, palpitation. DIGESTIVE: Nausea. PSYCHIATRIC: Depression. SKIN: Hypersensitivity, including localized and generalized rash. RESPIRATORY: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure. ENDOCRINE: Masked symptoms of hypoglycemia in insulin-dependent diabetics (see WARNINGS). SPECIAL SENSES: Signs and symptoms of keratitis, blepharoptosis, visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis. Other reactions associated with the oral use of non-selective adrenergic receptor blocking agents should be considered potential effects with ophthalmic use of these agents.

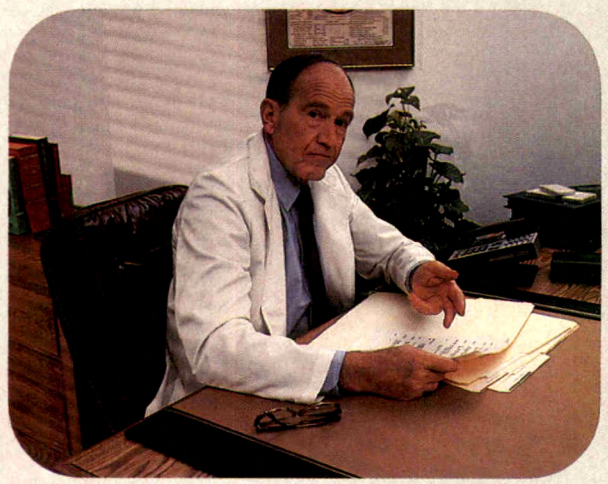
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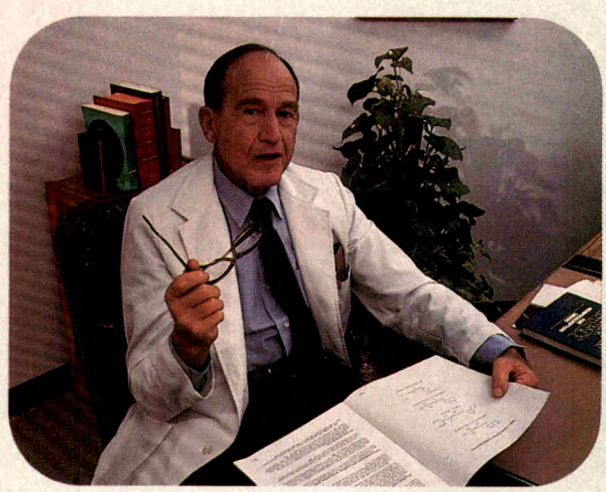
1 "Well, four years of clinical-study data convinced me levobunolol was safe and effective in chronic open-angle glaucoma and ocular hypertension . . ." *



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Please see adjacent page for brief summary of prescribing information.



*Levobunolol Clinical Study Group. Levobunolol: A beta-adrenoceptor antagonist effective in the long-term treatment of glaucoma. Ophthalmology 1985;92:1271.

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Imaging of Cerebral Blood Flow and Metabolism in Amblyopia by Positron Emission Tomography

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We used positron emission tomography to study monocular visual activation of various brain regions in four amblyopic and two normally sighted adults. Imaging of relative cerebral blood flow using the tracer $H_2{}^{15}O$ showed reduced activation of primary visual cortex by the amblyopic as compared with the sound eye. Imaging of relative cerebral glucose metabolism using the tracer [^{18}F]-2-deoxyglucose showed equal activation of primary visual cortex by either eye in the control subject, but reduced activation of primary and accessory visual cortex by the amblyopic as compared with the sound eye in two amblyopic subjects. Relative glucose metabolism was consistently higher in the frontal and temporal lobes contralateral to the viewing eye, both in normal and amblyopic subjects.

AMBLYOPIA is a unilateral or bilateral decrease of visual acuity for which no structural cause can be detected on physical examination of the eye. It is caused by form vision deprivation or abnormal binocular interaction in early childhood. Strabismus, anisometropia, and congenital cataracts are common causes of amblyopia.[1]

Experimental amblyopia can be induced in kittens and infant monkeys by unilateral eyelid suturing,[2] optically induced anisometropia,[3] and surgically induced strabismus.[4] By using microelectrode techniques, it has been determined that the number of visual cortical neurons that can be activated by visual stimulation of the amblyopic eye is reduced, and that most visual cortical neurons respond only to stimulation of the sound eye.[5] Shrinkage of cells in layers of the lateral geniculate nucleus connected to the amblyopic eye has been noted in animals,[6-8] as well as in one amblyopic human.[3]

While extensive developmental anatomic studies have been performed in amblyopic animals, these data are only presumed to be applicable to humans. With the exception of one autopsy study in which the lateral geniculate nuclei were examined,[3] neuroanatomic studies of amblyopic patients have not yet been done to confirm the structural basis of amblyopia in humans.

New techniques of neurophysiologic investigation offer promise in the study of visual processing in the brain. The technique of autoradiography consists of administration of a biochemical labeled with a radioactive isotope; the biochemical is taken up by tissues at a rate determined by metabolic activity, which is in turn tightly coupled to functional activity.[9] Using [^{14}C]deoxyglucose as a tracer for the rate of tissue glucose metabolism, this technique has demonstrated metabolic activation by visual stimulation of the geniculate and oculomotor nuclei, as well as primary visual cortex, in laboratory animals.[9]

The technique of autoradiography is not suitable to human studies, for it requires that the

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animals be killed and the tissues of interest be fixed and sectioned. Positron emission tomography, a recently developed nuclear medicine imaging technique, allows the application of strategies similar to the autoradiographic technique in a noninvasive way in human subjects.[10] Various compounds can be labeled with positron emitters for the study of various biochemical and functional characteristics of the brain.[11] The fundamental principle underlying positron emission tomography is the localization within tissues of unstable isotopes that decay by emitting positrons, antimatter electrons carrying a positive charge. Positrons encounter and annihilate ubiquitous tissue electrons, converting their rest masses into pairs of 511-keV gamma photons that travel in opposite directions to readily exit the tissues, where they can be imaged by external detector arrays.[11] Computerized imaging techniques reconstruct the tissue location of radiopharmaceuticals labeled with positron-emitting isotopes.[11,12]

The glucose analogue 2-deoxyglucose can be labeled with the positron emitter fluorine[18] to produce [^{18}F]-2-deoxyglucose, a tracer well suited to the study of glucose metabolism with positron emission tomography.[13] Since the half-life of ^{18}F is only 109.7 minutes, this isotope must be produced in a cyclotron and rapidly subjected to chemical reaction and purification to produce a useful radiotracer.[14] However, this short half-life can be an advantage, for it greatly reduces the duration of radiation exposure to a subject receiving [^{18}F]fluorodeoxyglucose. Studies using [^{18}F]fluorodeoxyglucose can be repeated in the same subject on consecutive days. The validity of measurements of regional brain glucose metabolism by positron emission tomography using [^{18}F]fluorodeoxyglucose has been demonstrated.[15]

The positron emitter ^{15}O has a half-life of only 2.07 minutes.[14] This isotope can be administered as $H_2{}^{15}O$ for the study of regional tissue blood flow with positron emission tomography.[10] The extremely short half-life of ^{15}O permits multiple imaging studies in the same subject on the same day, making the tracer ideally suited for experimental designs involving physiologic activation procedures.

Positron emission tomography has been extensively used to investigate cognitive and sensory function in humans. Regional cerebral activation as a result of audition, vision, and tactile stimulation, as well as cognitive tasks, has been demonstrated.[16,17] In particular, investigators have imaged human visual cortex using [^{18}F]fluorodeoxyglucose, demonstrating significant progressive increases in the local metabolic rate for glucose in visual cortex with increases in visual stimulus complexity or the opening of the second eye.[18,19] Topographic activation of particular regions of visual cortex has been demonstrated in response to stimulation of a visual hemifield,[20] and to limitation of the visual stimulus to particular regions of the visual field.[19,21,22] Functional imaging studies of the visual cortex in amblyopic humans have not yet been performed.

Since the emerging laboratory evidence implicates amblyopia as a disorder of the visual part of the brain, we applied positron emission tomography for functional imaging of cerebral blood flow and glucose metabolism in amblyopic humans. Our goals included demonstration of the feasibility of positron emission tomography in the study of amblyopia, as well as evaluation of the possible roles of accessory visual cortex and those cortical areas traditionally regarded as uninvolved in vision.

Subjects and Methods

Six right-handed, adult volunteer subjects participated in this study (Table). Four were amblyopic, having best corrected visual acuities in the amblyopic eye of 20/200 or less, and 20/20 or better in the fellow eye. Two subjects were normally sighted controls having visual acuities of 20/15 or better in each eye, and normal stereopsis. All subjects underwent a complete ocular examination, including refraction and examination of the fundus with dilated pupils.

All subjects gave written informed consent after the purposes, risks, and benefits of this study were explained in detail. Persons under 18 years of age and women of child-bearing age were excluded. Patient 3 was included because she had previously had a hysterectomy. This study was conducted under protocols approved by the Radioactive Drug Research Committee of the University of Texas Health Science Center at Houston, and institutional review boards for protection of human subjects of the University of Texas Health Science Center at Houston, Baylor College of Medicine, and Texas Children's Hospital.

All radiopharmaceuticals were prepared at the cyclotron facility of the Positron Diagnostic

TABLE
CHARACTERISTICS OF SUBJECTS UNDERGOING POSITRON EMISSION TOMOGRAPHY

SUBJECT NO., AGE (YRS), SEX	VISUAL ACUITY (REFRACTION) R.E.	VISUAL ACUITY (REFRACTION) L.E.	AFFERENT PUPILLARY DEFECT	DIAGNOSIS
1, 25, M	20/15 (−4.75 +0.75 × 92)	20/15 (−6.25 +1.00 × 90)	No	Myopia
2, 60, F	20/20 (−2.50 +1.00 × 180)	20/400 (−5.24 +6.00 × 75)	No No	Occlusion amblyopia from complete congenital blepharoptosis
3, 33, F	20/20 (+1.25 +0.50 × 95)	20/800 (+7.50 +2.50 × 30)	Yes	Deprivation amblyopia, despite congenital cataract extraction at age 6 years, mild bilateral optic atrophy
4, 23, M	20/15 (−1.50 +1.00 × 110)	20/15 (−1.50 +1.00 × 70)	No	Myopia
5, 20, M	20/200 (−10.00 +1.50 × 15)	20/20 (+0.75 sph)	No	Anisometropic amblyopia
6, 27, M	20/20 (−2.50 sph)	20/400 (−1.25 sph)	No	Strabismic amblyopia from infantile esotropia

and Research Center of the University of Texas Health Science Center at Houston. The isotope ^{15}O was produced using the $^{14}N(d,n)^{15}O$ reaction by bombarding a 1% mixture of molecular oxygen in nitrogen with 8-MeV deuterons generated in the cyclotron. The resulting gas was exchanged with ^{16}O to produce $^{15}O^{16}O$, which was mixed with molecular hydrogen and passed over a palladium catalyst at a temperature of 300 C, producing $H_2{}^{15}O$ vapor. The $H_2{}^{15}O$ vapor was bubbled through physiologic saline and dispensed through a 0.22-μm filter, which rendered the solution sterile and nonpyrogenic.

The isotope ^{18}F was produced using the $^{18}O(p,n)^{18}F$ reaction by bombarding commercially available $H_2{}^{18}O$ with 16-MeV protons generated in the cyclotron. The synthesis of [^{18}F]fluorodeoxyglucose from ^{18}F is complex and has been described in detail.[23] The ^{18}fluorodeoxyglucose was also purified and sterilized after synthesis, rendering it nonpyrogenic.

Positron emission tomography imaging was performed using a positron tomograph designed and constructed at the University of Texas Health Science Center at Houston. The tomograph consists of a scintillation array and a computer for data recording and image reconstruction. The camera contains an array of 720 cesium fluoride scintillation detectors, each measuring 18 mm in diameter and 45 mm in length, arranged in five rings of 144 detectors each. For a uniform source 20 cm in diameter filled with 1 mCi/ml of radioactivity, the sensitivity of the tomograph has been measured at 10,000 counts/second for the outer slices and more than 26,000 counts/second for the inner five slices.[24] To improve linear sampling, the scintillation detectors execute a circular orbital motion over a diameter of 19.6 mm at a rate of 1 oscillation/second. This entire arrangement enables the acquisition of nine image planes simultaneously, at a spatial resolution of 12 to 14 mm (full width at half maximum).[24] Image processing was performed using a DEC VAX 11/750 digital computer and an array of 20 fast bit-slice microprocessors.

For positron emission tomography subjects lay supine on a gantry, with their heads firmly strapped into a padded head holder made of acrylic plastic. The camera was oriented either in the vertical plane, or was tilted at 15 to 17 degrees from the vertical to parallel the base of the brain. A laser on the positron camera pro-

jected reference lines onto the subject's head; a surgical skin marking pen was used to mark the positions of the reference lines on subjects' faces for accurate repositioning on repeated scans.

Before positron emission scans on each day of testing, an attenuation image of the head was obtained for each subject using a gallium[68] ring source. This attenuation image was used to correct emission images for absorption of radiation by superficial cranial structures.

All studies were conducted at the same time of day. Subjects were instructed to omit lunch before scanning, although most fasted from the midnight before. A peripheral intravenous line was placed and kept open with a slow infusion of isotonic saline. Before administration, radioactivity levels in each dose of tracer were measured in duplicate using different radiation counters.

Relative blood flow imaging—Cerebral blood flow was imaged in two amblyopic subjects and one control subject using a modification of the $H_2{}^{15}O$ intravenous bolus injection technique.[25] Scanning was started immediately after injection of 30 to 40 mCi of $H_2{}^{15}O$ and was continued for three minutes. Subjects were scanned sequentially during visual stimulation with a strobe light flashing at 8 Hz, since other investigators have demonstrated that this photic stimulation rate produces maximal activation of cerebral blood flow.[26,27] Subjects wore their distance refractive correction in a trial frame, and one or both eyes were covered with a densely occlusive patch as dictated by the protocol. The visual stimulus was presented in a dimly lit room for one minute before tracer injections and was continued for a total stimulation time of three minutes. During scanning, noise was kept to a minimum and subjects were requested to refrain from moving or speaking.

For each scan, $H_2{}^{15}O$ was injected intravenously in 5 to 10 ml of isotonic saline. The tracer was followed by a bolus of 10 ml of saline. After correction for attenuation, cumulative counts acquired by the camera in the entire three-minute period were used to reconstruct digital images of relative regional blood flow.

Relative glucose metabolism imaging—Relative glucose metabolism was measured in two amblyopic subjects and one control subject using an intravenous bolus injection of 5 to 8 mCi of [^{18}F]fluorodeoxyglucose. Subjects were tested on two consecutive days, first with the left eye and then with the right eye occluded. Visual stimulation was obtained using a dramatic entertainment video motion picture with sound track; the display subtended a horizontal angle of 28 degrees at a viewing distance of 50 cm. The visual stimulus was presented for 35 minutes after injection of [^{18}F]fluorodeoxyglucose. Subjects wore refraction correction in a trial frame while viewing the visual stimulus. After visual stimulation, subjects were repositioned in the camera for scanning over the next 25 minutes. This repositioning was achieved using reference marks on the skin. The same tracer dose was used for each of the two sequential studies. Images of relative cerebral glucose metabolism were corrected for attenuation and digitally reconstructed.

Reconstructed images were photographed and placed on magnetic media for storage. Regions of interest were defined according to standard neuroanatomy and were drawn directly on the reconstructed images.[28,29] The average number of radioactive counts was determined for eight regions of interest, corresponding to the left and right frontal lobes, the left and right temporal lobes, the left and right thalamus, primary visual cortex (located on the midline near the occipital pole), and accessory visual cortex (located on the midline anterior and superior to primary visual cortex). Average radioactive counts were also determined for the entire brain image slice in which region-of-interest analysis was performed.

Relative values were obtained by dividing the average number of counts within the region of interest by the average number of counts in the entire brain slice. Relative values increase the sensitivity of the method because they compensate for intersubject and intrasubject variability,[30] and have been shown to be well suited to demonstration of regional activation caused by stimulation.[31] In this study, values in regions of interest relative to the whole brain slice are referred to as cortical activation ratios.

Results

Blood flow imaging—One normally sighted control subject (Subject 1) underwent relative cerebral blood flow imaging with stroboscopic visual stimulation. The testing was performed under conditions of monocular stimulation of each eye separately to determine if the two normal eyes can activate the brain equally. We found similar blood flow in primary visual

cortex during stimulation of each eye (Fig. 1). Quantitation of this effect shows that for the right eye viewing, the cortical activation ratio for primary visual cortex was 1.38 and for the left eye viewing, it was 1.37. Although no level of statistical significance can be calculated for cortical activation ratios, this difference is small and probably not meaningful. With both eyes patched (not shown in Figure 1), the cortical activation ratio was 1.23, a much lower value than with either eye viewing. Thus, relative blood flow in primary visual cortex of a normally sighted subject was activated similarly by visual stimulation of either eye.

Two amblyopic subjects underwent relative cerebral blood flow imaging during stroboscopic visual stimulation. Subject 2 has diabetes with hypercholesterolemia and was taking a beta-blocking antihypertensive medication. Scans were performed once with the sound right eye viewing, and again with the amblyopic left eye viewing (Fig. 2). During visual stimulation of the amblyopic left eye (Fig. 2, left) there was a small area of high blood flow along the interhemispheric fissure in primary visual cortex. There was little blood flow in more lateral visual cortex and in frontal and temporal regions. Conversely, during visual stimulation of the sound right eye (Fig. 2, right) there was an extensive area of high blood flow throughout primary visual cortex, as well as greater blood flow in frontal and temporal regions. The cortical activation ratio for medial frontal cortex was 1.18 with the sound eye viewing, and 1.13 with the amblyopic eye viewing. Additionally, during visual stimulation of the sound right eye there was high relative blood flow in the posterior parieto-occipital region thought to be responsible for processing of image motion, the temporal-occipital-parietal pit.[28] This was seen as a small lobe of high blood flow flanking the region of primary visual cortex, particularly on the left side (Fig. 2, right).

Subject 3 is amblyopic but has no relevant medical history. Four scans of regional cerebral blood flow were performed during stroboscopic visual stimulation in sequence with the right eye viewing alone, with the left eye viewing alone, with both eyes viewing, and with neither eye viewing. With the sound right eye viewing (Fig. 3, right), there was high blood flow in primary visual cortex, corresponding to a cortical activation ratio of 1.35. With the amblyopic left eye viewing (Fig. 3, left), there was less activation of relative blood flow in primary visual cortex, with a cortical activation ratio of 1.31. With neither eye viewing (not shown), the cortical activation ratio decreased to 1.29, whereas it increased to 1.32 with both eyes viewing.

Glucose metabolism imaging—Relative glucose metabolism studies exhibit better anatomic resolution than those imaging relative blood flow. Normally sighted control Subject 4 underwent two scans of relative cerebral glucose metabolism. The first scan was performed after visual stimulation of the dominant right eye with a dramatic video motion picture. Active glucose metabolism was observed in primary visual cortex, with a cortical activation factor of 1.31. Region-of-interest analysis showed that the contralateral temporal lobes and thalamus were more active than the ipsilateral by 6% to 20%. The second scan for control Subject 4 was performed the next day, with visual stimulation of the nondominant left eye (Figs. 4 and 5, bottom). Again, active metabolism in primary visual cortex was evident, with a cortical activation ratio of 1.34. There was also about 10% greater glucose metabolism in the contralateral as compared with the ipsilateral frontal and temporal lobes, but not in the thalamus. A midline sagittal reconstruction of the brain (Fig. 5) showed the similarity of glucose metabolism in primary visual cortex during visual stimulation of the right and left eyes. For accessory visual cortex (area 19 of Brodmann),[28] the cortical activation ratio for the right eye was 1.29, whereas the cortical activation ratio was 1.50 for the left eye; this may represent a meaningful difference.

Subject 5 has anisometropic amblyopia, leading to a best corrected visual acuity of 20/200 in the amblyopic right eye. Comparison of scans for Subject 5 on consecutive days demonstrated greater glucose metabolism in primary visual cortex during viewing by the sound left eye (cortical activation ratio, 1.34) as compared with the amblyopic right eye (cortical activation ratio, 1.26). More striking was the degree of asymmetrically greater metabolism in the cerebral hemisphere opposite whichever eye was viewing (Fig. 6). With the amblyopic right eye viewing, the asymmetry was a result of 5% to 20% greater activation of the contralateral than the ipsilateral frontal and temporal lobes, but not the thalamus. With the sound left eye viewing, the asymmetry was evident in 10% to 15% greater activities in the contralateral as compared with the ipsilateral frontal and temporal lobes, but not the thalamus. The cortical activation ratio showed no appreciable differ-

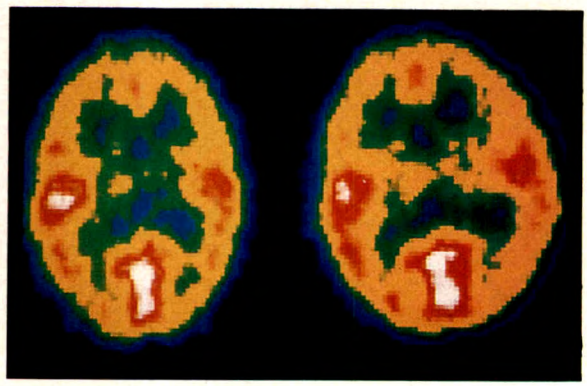


Fig. 1 (Demer and associates). Images of relative cerebral blood flow in a normally sighted subject during monocular stroboscopic stimulation of the left eye (left) and the right eye (right). Images are in the same plane as conventional axial computed tomographic scans. The left side of the image corresponds to the left side of the patient. With stimulation of either eye, there is equal activation of primary visual cortex, located on the midline at the bottom of each image and seen in white. Relative blood flow is coded using a false color scheme, so that areas of higher blood flow are shown in brighter colors, going from blue at minimum to white at maximum, according to the scale shown in Figure 4.

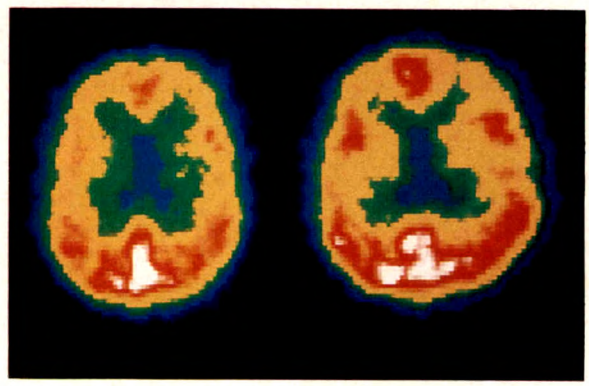


Fig. 2 (Demer and associates). Images of relative cerebral blood flow in Subject 2 during monocular stroboscopic stimulation of the amblyopic left eye (left) and sound right eye (right). Primary visual cortex appears in white at the bottom of each image, flanked by lobes of activity that may represent cortical motion processing areas. Activation of primary visual cortex is more extensive with stimulation of the right eye, for which there is also more extensive activation of the temporal-occipital-parietal pit (seen in white flanking primary visual cortex) and frontal (top, red) and temporal (upper left and right, red) regions.

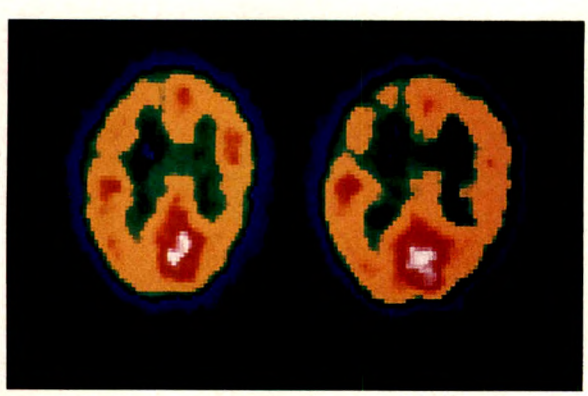


Fig. 3 (Demer and associates). Images of relative cerebral blood flow in Subject 3 during monocular stroboscopic stimulation of the amblyopic left eye (left) and the sound right eye (right). Primary visual cortex appears as an area of white, representing high blood flow, at the midline at the bottom of each image. There is significantly greater activation of blood flow in primary visual cortex during viewing with the sound right eye than with the amblyopic left eye.

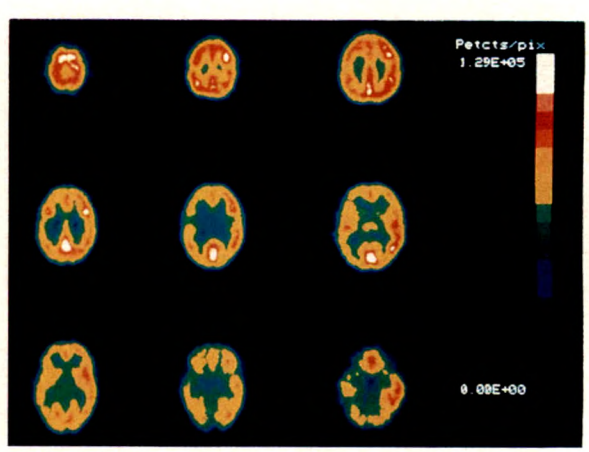


Fig. 4 (Demer and associates). Series of nine simultaneous images of relative cerebral glucose metabolism obtained in normally sighted control Subject 4, who was viewing a video motion picture with his left eye. Note active glucose metabolism in primary visual cortex, seen as a white area on the midline at the bottom of each of the middle row of three images. Note also the greater metabolism in the contralateral right hemisphere, seen as a preponderance of red on the right side of each image. The false color scale on the right shows the relative activity assigned to each color in decreasing fashion from top to bottom, and was used for all figures shown here.

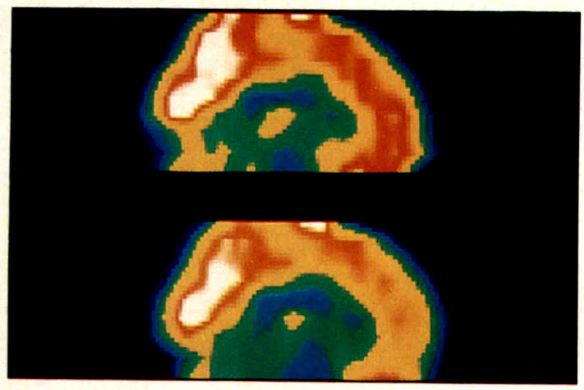


Fig. 5 (Demer and associates). Midline sagittal reconstructions of images of relative cerebral glucose metabolism in normally sighted control Subject 4 (obtained as in Fig. 4). Primary visual cortex is the white area of high glucose metabolism seen at the left, or occipital tip, of each image. The two images show equal activation of primary visual cortex during monocular viewing with the right (top) and left (bottom) eyes.

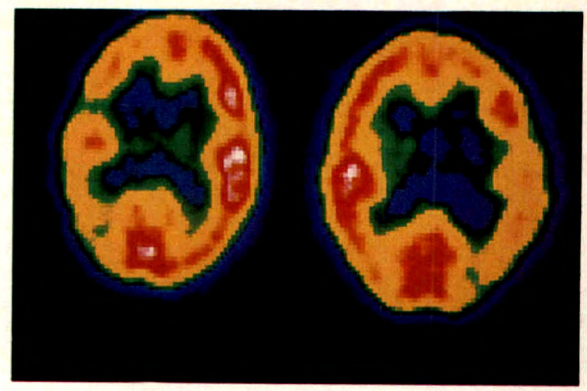


Fig. 6 (Demer and associates). Images of relative glucose metabolism in anisometropic amblyopic Subject 5, showing greater metabolism in primary visual cortex during monocular viewing of a video motion picture with the sound left eye (left) than with the amblyopic right eye (right). Primary visual cortex is seen as in Figures 1 and 3. Note greater activation of the contralateral cerebral hemisphere by either eye.

ence for accessory visual cortex between the two eyes (1.26 in both cases).

Subject 6 has strabismic amblyopia, leading to a best corrected visual acuity of 20/400 in the amblyopic left eye. This subject underwent imaging of relative glucose metabolism on two consecutive days, first with the sound right eye viewing, and later with the amblyopic eye viewing (Figs. 7 and 8). The axial images showed three findings (Fig. 7). First, primary visual cortex (area 17/18 of Brodmann)[28] was more metabolically active during viewing by the sound than by the amblyopic eye. With the sound eye viewing, the cortical activation ratio for primary visual cortex was 1.50; it was only 1.39 with the amblyopic eye viewing. This large difference demonstrates much greater glucose metabolism in primary visual cortex with the sound eye viewing. The cortical activation ratio for accessory visual cortex was 1.36 for visual stimulation of the sound right eye, and 1.41 for visual stimulation of the amblyopic left eye.

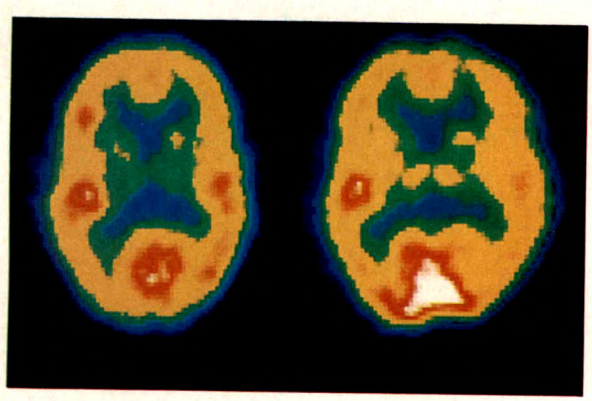


Fig. 7 (Demer and associates). Images of relative glucose metabolism in strabismic amblyopic Subject 6 (obtained as in Fig. 6). There is little glucose metabolism in primary visual cortex evident in the image at left, obtained during monocular viewing by the amblyopic left eye, while there is active glucose metabolism in primary visual cortex in the image at right obtained during viewing by the sound right eye. Note greater activation of the putative cortical motion processing region flanking primary visual cortex during viewing by the sound eye. With the right eye viewing, the left temporal lobe is more activated than the right.

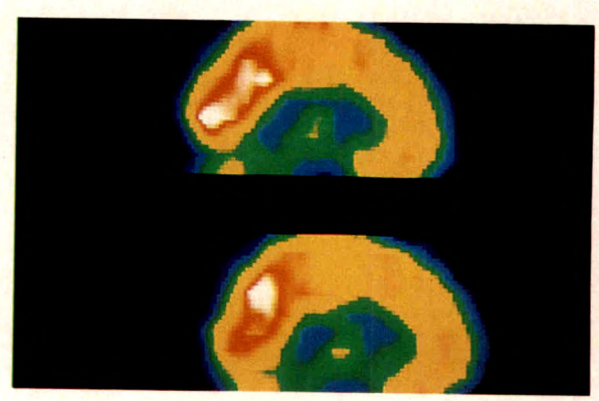


Fig. 8 (Demer and associates). Midline sagittal reconstruction of images of relative glucose metabolism in strabismic amblyopic Subject 6 (obtained as in Fig. 5). During viewing with the sound right eye (top), there is intense glucose metabolism in the occipital tip of primary visual cortex, with activity extending anterosuperiorly into areas 19 and 7. During viewing with the amblyopic left eye (bottom), there is little glucose metabolism in primary visual cortex, but there is activation of areas 19 and 7.

Second, each viewing eye tended to produce greater glucose metabolism in regions in the contralateral hemisphere. There was 16% greater glucose metabolism in the contralateral relative to the ipsilateral temporal lobe, but there was no asymmetry in the frontal lobe or thalamus evident during visual stimulation of the sound right eye. With the amblyopic left eye viewing, there was 5% to 10% greater glucose metabolism in the contralateral frontal and temporal lobes, but not the thalamus. Third, with the sound eye viewing, there was metabolic activity in the temporal-occipital-parietal pit (Fig. 7).

In a sagittal reconstruction of scans in Subject 6 (Fig. 8), there was a striking reduction in relative glucose metabolism in the occipital region during visual stimulation of the amblyopic compared with the sound eye. Glucose metabolism in cortical areas 19 and 7 of Brodmann[28] was relatively high, regardless of which eye was stimulated in this subject.

Discussion

Both types of functional brain imaging, relative cerebral blood flow and relative cerebral glucose metabolism, demonstrated greater activity in primary visual cortex during monocular visual stimulation of sound as compared with amblyopic eyes. Monocular visual stimulation of normal control eyes produced equal activation of primary visual cortex. However, monocular visual stimulation of either eye, in normal or amblyopic subjects, produced significantly greater glucose metabolism in the contralateral frontal and temporal lobes, and in one subject in the contralateral thalamus. In some subjects, blood flow or metabolic activity in the temporal-occipital-parietal pit, a putative cortical motion processing center, was observed during visual stimulation. These findings confirm in amblyopic humans what has been established by invasive methods in animal models: there is a significant reduction of neuronal activity in those parts of the visual cortex that are connected to the amblyopic eye.[5]

To our knowledge, the series of experiments reported here constitute the first use of positron emission tomography in the study of human amblyopia. Brain imaging was performed using $H_2{}^{15}O$ as an indicator of cerebral blood flow, and [^{18}F]fluorodeoxyglucose as an indicator of glucose metabolism. These measures have been demonstrated to correlate with neuronal activity.[32]

While positron emission tomography can be used to measure absolute levels of blood flow and glucose uptake in the human brain, such techniques require serial arterial blood sampling.[15,32] Since no arterial sampling was used in the present series of experiments, the images obtained represent only relative measures of cerebral blood flow and metabolism. This is adequate to substantiate our conclusions, for in the present experiments the subjects served as their own controls under varying conditions of visual stimulation, and the cortical activation ratios reported here would not be confounded by minor systemic metabolic variations. Relative regional cerebral glucose metabolism measurements have been shown to have a test/retest reproducibility for individual subjects of less than 1%,[33] substantially less than the differences we observed between stimulation of sound vs amblyopic eyes. Further, quantitative analysis of cerebral regions of interest permits strong conclusions about asymmetry of relative activation of individual brain structures, since systemic metabolic factors cannot influence these comparisons. In amblyopic Subjects 5 and 6, relative glucose metabolism in primary visual cortex was 6% to 8% higher with the sound than with the amblyopic eye viewing. Such values are within the range of asymmetries (8% ± 3%) for left and right visual cortex reported for experiments in normal humans in whom only half of the visual field is stimulated, so that the visual cortex corresponding to the stimulated hemifield is more active than that corresponding to the unstimulated hemifield.[20,34]

Our studies of relative cerebral blood flow demonstrated that the primary visual cortex of a normally sighted subject can be significantly activated by stroboscopic visual stimulation of either eye. These studies were conducted using a three-minute duration of scanning after injection of the $H_2{}^{15}O$ tracer. Although it has been argued that this relatively long scanning duration causes an underestimation of differences in cerebral blood flow (particularly between gray and white matter),[25,35] it has also been pointed out that scans of short duration may overestimate cerebral blood flow because of the effects of the arterial blood volume fraction and differences in arrival time of the tracer bolus across the brain.[36] Although the optimal duration of scanning may be controversial, longer scans improve the statistical accuracy of reconstructed images and decrease certain biases.[36] Expert opinion supports the view that the optimal imaging time is dependent upon the tomo-

graph used, the tracer dose, and composition of the tissue under study.[35] Such considerations are crucial only to the precise quantitative determination of absolute levels of tissue blood flow, so that it remains valid to use our technique to study relative differences in cerebral blood flow in subjects serving as their own controls under different conditions of visual stimulation. However, shorter scan durations might show even larger or additional differences in regional blood flow resulting from stimulation of amblyopic vs sound eyes. We are continuing to investigate this issue.

In Subject 3, stroboscopic stimulation of the sound eye produced greater activation of blood flow in primary visual cortex than did stimulation of the severely amblyopic eye. In Subject 2, stimulation of the sound eye produced activation of cerebral blood flow in a more extensive region of visual cortex than did stimulation of the amblyopic eye, although for the amblyopic eye peak relative blood flow in a small region near the midline was higher than in a similar region for the sound eye. Greater activation of blood flow in frontal and temporal regions was demonstrated during stimulation of the sound than of the severely amblyopic eye for Subject 2. In this subject, a hypertensive diabetic with hypercholesterolemia who was taking a beta-blocking agent to control arterial blood pressure, cerebrovascular disease and vasoactive drugs probably altered the vasoregulatory response to visual stimulation; the anticipated effect of this artifact would be to blunt the enhancement of blood flow by physiologic stimulation. Perhaps these effects accounted for the differences in activation of blood flow in primary visual cortex in this subject. It can be concluded, however, that the effect on primary visual cortex of amblyopia can be detected by positron emission tomography scanning using $H_2{}^{15}O$. Effects of amblyopia on frontal cortex are also plausible, particularly in light of evidence that precentral cortical visual-evoked potentials are more severely reduced in amblyopia than are occipital-evoked potentials.[37] This intriguing possibility merits further investigation.

Our studies of relative glucose metabolism demonstrated that primary visual cortex of a normally sighted subject is activated equally by the monocular viewing of a video motion picture using either eye. In normally sighted Subject 4, and amblyopic Subjects 5 and 6, the frontal and temporal lobes contralateral to the viewing eye were significantly more activated than the ipsilateral structures by monocular visual stimulation. This finding is surprising since the optic chiasm of humans is anatomically about equally decussated, with projections from each eye to both sides of the brain. The finding of greater activation of the frontal and temporal lobes contralateral to the viewing eye implies that the afferent visual pathway may be decussated to a greater degree when assessed by functional methods than by anatomic methods. Other investigators have used positron emission tomography to demonstrate symmetric activation of left and right visual cortex of monocularly viewing normal subjects, but did not report hemispheric asymmetries.[19] These investigators may not have carefully evaluated hemispheric asymmetries, or the random-pattern visual stimulus that they used may have produced a different type of cerebral activation than did the complex motion picture stimulus used in the present study. Conceivably, cognitive processing of complex monocular visual input may be predominantly in the contralateral cerebral hemisphere. This suggestion requires confirmation and further investigation. We have no explanation for the greater activation of accessory visual cortex by visual stimulation of the left eye than the right eye in Subject 4.

Imaging of relative cerebral glucose metabolism in anisometropic amblyopic Subject 5 and strabismic Subject 6 both demonstrated significantly greater glucose metabolism in primary visual cortex during viewing with the sound as compared with the amblyopic eye. Similar findings were present in imaging of relative cerebral blood flow in Subject 3 with deprivation amblyopia. This suggests that, despite differences in the pathogenesis of amblyopia from patient to patient, a common characteristic of amblyopia is reduction in processing of visual information from the amblyopic eye.

Positron emission tomography in Subjects 2 and 6 demonstrated activity in a posterior parieto-occipital region flanking primary visual cortex, the temporal-occipital-parietal pit. This region, present bilaterally,[28] has been shown to be activated by a low-contrast, moving stimulus.[38] The finding that infarction of the temporal-occipital-parietal pit produces a syndrome of selective deficits in visual motion detection makes this cortical region a likely candidate for a cortical motion detection center.[39] It is uncertain why activation of the temporal-occipital-parietal pit was not observed in all subjects. For subjects undergoing stroboscopic stimulation, there may have been insufficient motion in the visual stimulus. For

the other two subjects undergoing visual stimulation with the video motion picture, this small cortical region may have been between imaging planes and thus not observed in the positron emission tomography scans. Activation of the temporal-occipital-parietal pit may also depend upon individual eye movement patterns of subjects viewing the visual stimulus. The role of the temporal-occipital-parietal pit in visual processing merits further investigation.

These studies have indicated that positron emission tomography is feasible for the investigation of brain function in human amblyopia. Amblyopia appears to affect visual processing in primary visual cortex, as well as other regions, such as accessory visual cortex, that receive visual information relayed from primary visual cortex. However, as seen in Figure 8, accessory visual cortical area 19, as well as area 7, continue to have relatively high glucose metabolism during viewing by the amblyopic eye. This may reflect either high basal metabolism in these areas, or perhaps continued visual processing despite failure to activate primary visual cortex.

Positron emission tomography has major advantages over evoked potential testing of the visual system, since it offers much greater spatial resolution as well as the ability to give three-dimensional information about the activity of deep brain structures.[18] Cortical visual-evoked potentials have provided little new information about the visual system because of these factors, as well as technical variability and problems in correlation with cortical neurophysiology.[18] In particular, the visual-evoked potential has been found to be subject to large variability, and to correlate poorly with local cerebral glucose metabolism.[19] Positron emission tomography could eventually be used as a superior objective method of documenting visual function, but the greatest value of this technique probably lies in its use in locating and characterizing the poorly understood extrastriate regions involved in vision. This technique has great potential for further research.

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Penetrating Keratoplasty for Pseudophakic Bullous Keratopathy After Extracapsular Cataract Extraction

Steven B. Koenig, M.D., and Richard O. Schultz, M.D.

Seventeen women underwent simple penetrating keratoplasty for pseudophakic bullous keratopathy after extracapsular cataract extraction. Corneal edema occurred an average of eight months after cataract surgery (range, zero to 32 months). Of 17 corneal grafts, 16 (94%) have remained clear during an average follow-up period of 14 months (range, two to 32 months). One eye had a nonimmunologic graft failure. Of 16 eyes with clear grafts, 14 (87%) achieved a visual acuity of 20/40 or better after surgery. Two eyes with a visual acuity of 20/50 and 20/200 had opacified posterior capsules and one demonstrated age-related macular degeneration. One eye with a postoperative visual acuity of 20/40 demonstrated cystoid macular edema. Fifteen of 17 contralateral eyes showed slit-lamp evidence of endothelial dystrophy.

PSEUDOPHAKIC BULLOUS KERATOPATHY has become the leading indication for penetrating keratoplasty in the United States.[1,2] The incidence of pseudophakic bullous keratopathy after intracapsular cataract extraction has been reported as high as 6%.[3] In contrast, the incidence of corneal edema after extracapsular cataract extraction and posterior chamber lens insertion has been estimated to be less than 1%, which reflects improvements in surgical technique, intraocular lens design, and the use of viscoelastic substances.[2] Previously published reports of penetrating keratoplasty for pseudophakic bullous keratopathy have indicated a high anatomic success rate (clear grafts) but poor visual results, primarily because of cystoid macular edema.[4-8] However, most of these eyes had undergone intracapsular cataract extraction with insertion of an anterior chamber or iris plane intraocular lens. The purpose of this study is to report the results of penetrating keratoplasty for pseudophakic bullous keratopathy associated with extracapsular cataract extraction and posterior chamber lens implantation.

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Patients and Methods

We reviewed retrospectively the records of 17 patients who underwent penetrating keratoplasty for pseudophakic bullous keratopathy associated with extracapsular cataract extraction at our institution between April 1984 and October 1987. Penetrating keratoplasty was performed by one of us (S.B.K.), and no patients were excluded from the study.

Surgery was performed under monitored anesthesia and included an O'Brien or Van Lindt facial nerve block and retrobulbar block using a 1:1 mixture of 2% lidocaine and 0.75% bupivacaine. Each patient received intravenous mannitol 20% (1 mg/kg of body weight) one hour before surgery. One drop of pilocarpine 2% was given preoperatively. A Honan balloon was placed on the globe (30 mm Hg) for 30 minutes before surgery. A single Flieringa ring was sutured to the episclera with four interrupted 6-0 black silk sutures. The donor corneal button was punched from the endothelial side of the donor cornea using a 7.75- or 8.0-mm disposable Castroviejo trephine and Polack punch. Donor corneas had been stored in McCarey-Kaufman or K-Sol media. The host cornea was incised two-thirds depth with a 7.5-mm trephine. After excision of the host cornea with Katzin scissors, sodium hyaluronate was placed on the surface of the iris and posterior chamber lens. The posterior chamber lens implant was left in place in each case; no vitrectomy was performed. The donor corneal

button was sutured with either 16 interrupted 10-0 nylon sutures or a double running 10-0 and 11-0 suture using 12 bites. Residual sodium hyaluronate was not removed from the anterior chamber and patients received one drop of timolol maleate and intravenous acetazolamide prophylactically immediately after surgery. Postoperatively, eyes were treated with frequent topical corticosteroids, cycloplegics, and antibiotics. Low-dose topical corticosteroids were continued indefinitely.

We recorded the results of refraction and slit-lamp examination from the most recent office visit. Spectacle visual acuity was measured with a trial frame. Best corrected visual acuity was measured by refracting over a plano power hard contact lens. Anisometropia was calculated by subtracting the spherical equivalent refractive error of the operated on eye from the spherical equivalent refractive error of the contralateral eye. Beginning at three months postoperatively, interrupted and running 10-0 nylon sutures were selectively removed to reduce postoperative corneal astigmatism. A clear graft designates an intact epithelium, compact stroma, no folds in Descemet's membrane, and a clear view of iris and anterior segment details. Cystoid macular edema and age-related macular degeneration were diagnosed using slit-lamp biomicroscopy and a 90-diopter lens. Posterior capsulotomies were performed with an Nd:YAG laser.

Results

All patients in this study were women (Table 1). The average age at the time of penetrating keratoplasty was 74 years. In each case, planned extracapsular cataract extraction and posterior chamber intraocular lens insertion were performed by another experienced surgeon. Two eyes (Patients 1 and 6) underwent phacoemulsification. The average interval between extracapsular cataract surgery and the onset of corneal edema was approximately eight months. Two eyes (Patients 3 and 12) developed opacified posterior capsules and underwent YAG laser capsulotomy before penetrating keratoplasty; the posterior capsules remained intact in the other 15 eyes. One eye (Patient 16) underwent repositioning of the posterior chamber lens implant two months after cataract surgery. Three eyes had preexisting chronic open-angle glaucoma (Patients 1, 2, and 16) and one eye (Patient 16) had previously undergone trabeculectomy. Two patients (Pa-

TABLE 1
PREOPERATIVE CLINICAL DATA

PATIENT NO., AGE (YRS), SEX	ONSET OF CORNEAL EDEMA	OCULAR HISTORY	CONTRALATERAL EYE
1, 75, F	7 mos	Glaucoma	+2 Guttata, glaucoma
2, 86, F	6 mos	Glaucoma	Fuchs' dystrophy
3, 81, F	9 mos	YAG capsulotomy	+2 Guttata
4, 73, F	Immediately	None	+4 Guttata, pseudophakia
5, 82, F	8 mos	None	+1 Guttata
6, 69, F	Immediately	None	Normal
7, 76, F	Immediately	None	+1 Guttata
8, 63, F	4 mos	Chorioretinitis	Normal
9, 69, F	8 mos	None	+3 Guttata
10, 80, F	Immediately	None	+3 Guttata
11, 59, F	Immediately	None	+2 Guttata
12, 74, F	30 mos	YAG capsulotomy, Fuchs' dystrophy	Fuchs' dystrophy, aphakic contact lens
13, 86, F	Immediately	None	+2 Guttata
14, 82, F	12 mos	None	+3 Guttata
15, 64, F	12 mos	None	+2 Guttata, pseudophakia
16, 66, F	32 mos	Glaucoma, trabeculectomy, reposition implant	+2 Guttata, glaucoma, trabeculectomy
17, 77, F	Immediately	Fuchs' dystrophy	Fuchs' dystrophy

TABLE 2
POSTOPERATIVE CLINICAL DATA

PATIENT NO.	GRAFT	MANIFEST REFRACTION	VISUAL ACUITY		LENGTH OF FOLLOW-UP (MOS)	COMMENTS
			SPECTACLE	BEST CORRECTED*		
1	Failed	−0.50 +3.75 × 130	20/400	20/400	32	Postoperative relaxing incision, trabeculectomy
2	Clear	−1.50 +4.50 × 70	20/50−2	20/25−2	34	Postoperative trabeculectomy
3	Clear	−3.50 +1.75 × 70	20/30−2	20/30	14	—
4	Clear	−2.75 +2.00 × 170	20/30−1	20/20−2	21	—
5	Clear	−4.00 +3.00 × 160	20/40	20/30	32	—
6	Clear	Unable	20/400	20/200	16	Opacified posterior capsule
7	Clear	−3.00 +3.75 × 173	20/40	20/40	17	Opacified posterior capsule
8	Clear	+0.50 +4.00 × 180	20/60	20/50+1	13	Age-related macular degeneration, opacified posterior capsule
9	Clear	+2.25 +2.50 × 45	20/20	20/20	22	—
10	Clear	−2.25 +2.50 × 90	20/60	20/40	7	Cystoid macular edema
11	Clear	+2.00 +1.50 × 3	20/50	20/40	6	YAG capsulotomy
12	Clear	−2.25 +6.50 × 180	20/80+1	20/30−2	4	—
13	Clear	+1.75 +2.50 × 165	20/30−1	20/30−1	11	—
14	Clear	+0.50 +2.50 × 45	20/25	20/25	4	Homograft rejection
15	Clear	−4.00 +3.25 × 7	20/20+3	20/20+3	4	—
16	Clear	−4.25 +2.25 × 135	20/60	20/30−2	4	—
17	Clear	−4.00 +5.75 × 176	20/50	20/25	2	—

*Hard contact lens refraction.

tients 12 and 17) were known to have Fuchs' dystrophy.

Of 17 grafts, 16 have remained clear during an average postoperative period of 14 months (range, two to 34 months) (Table 2). Patient 1, who underwent a corneal relaxing incision and trabeculectomy, developed nonimmunologic graft failure 32 months after penetrating keratoplasty. One eye (Patient 14) developed a mild immunologic homograft rejection two months after surgery; the rejection episode was treated successfully with frequent topical corticosteroids, and the graft has remained clear.

The average best corrected visual acuity in eyes with clear grafts was approximately 20/45; the median visual acuity was 20/30. The average spectacle-corrected visual acuity was approximately 20/65; the mean cylinder correction was 3 diopters. Postoperative anisometropia ranged from 0 to 8.50 diopters (mean, 2.4 diopters). Four eyes had postoperative anisometropia exceeding 3 diopters. Three of these patients (Patients 8, 9, and 10) had immature senile cataracts in the contralateral eye and were not bothered by aniseikonia.

Of 16 eyes with clear grafts, 14 achieved a postoperative visual acuity of 20/40 or better. Only one patient (Patient 6) achieved 20/200 or less, which was attributed to an opacified posterior capsule that could not be opened with the Nd:YAG laser. The patient declined surgical discission. Two eyes (Patients 7 and 8) developed mildly opacified posterior capsules but have not undergone YAG laser capsulotomy.

One eye (Patient 10) showed clinically recognizable signs of intraretinal cystic changes and retinal edema early in the postoperative period after penetrating keratoplasty. One eye (Patient 8) had drusen and rarefaction of the retinal pigment epithelium consistent with age-related macular degeneration.

One eye (Patient 1) demonstrated high postoperative corneal astigmatism and subsequently underwent a corneal relaxing incision. Patients 1 and 2 had increased intraocular pressure postoperatively that could not be controlled with maximum medical therapy. Both eyes underwent trabeculectomy, with subsequent control of the pressure.

Of the 17 contralateral eyes, 15 demonstrated

slit-lamp evidence of endothelial disease. Fourteen eyes exhibited corneal guttata on specular reflection. One eye (Patient 2) showed frank corneal edema with epithelial bullae, subepithelial pannus formation, and folds in Descemet's membrane. Four of the contralateral eyes had undergone previous intraocular surgery (Patients 4, 12, 15, and 16) and three were aphakic.

Discussion

Our findings suggest that pseudophakic bullous keratopathy after extracapsular cataract extraction has a better prognosis for visual recovery after corneal transplanation than does pseudophakic bullous keratopathy after intracapsular cataract extraction. Previously published series have documented excellent anatomic results, with 80% to 90% of grafts remaining clear in the early postoperative period.[2,4,9] However, most of the patients undergoing penetrating keratoplasty after intracapsular surgery had poor postoperative visual acuity as a result of cystoid macular edema. Waring and associates[7] reported that 28% of patients achieved a visual acuity of 20/40 or better after penetrating keratoplasty with intraocular lens removal. Kozarsky and colleagues[8] reported that 38% of eyes with clear grafts and retained intraocular lens implants achieved a visual acuity of 20/40 or better after keratoplasty. However, they also noted that three of four patients with pseudophakic bullous keratopathy and posterior chamber lens implants had a visual acuity of 20/40 or better after keratoplasty. In the present study, 16 of 17 eyes (94%) maintained clear grafts and 14 of 16 eyes with clear grafts (87%) achieved this level of visual acuity during the postoperative follow-up period.

Cystoid macular edema has been reported as the most common cause of poor visual acuity after penetrating keratoplasty for pseudophakic bullous keratopathy.[4-6] Macular edema has been attributed to the intracapsular cataract surgical technique, intraocular lens-induced uveitis, and excessive surgical trauma during penetrating keratoplasty. In this series, however, only one patient showed clinically recognizable signs of cystoid macular edema, which were probably present before penetrating keratoplasty. The low incidence of cystoid macular edema may have been because all patients had undergone extracapsular cataract extraction with preservation of the posterior capsule. Jaffe, Clayman, and Jaffe[10] demonstrated a lower incidence of angiographically proven cystoid macular edema after uncomplicated extracapsular cataract extraction than after intracapsular cataract extraction. Aside from corneal edema, eyes in this series showed minimal disease. Since posterior chamber lens implants were retained, mechanical vitrectomy was not required and surgical manipulation of anterior segment structures was minimized.[11]

Of 17 grafts in this series, 16 remained clear during the postoperative follow-up period. The low incidence of graft failure can be attributed to the absence of poor prognostic host factors[12] and to the relatively short postoperative follow-up interval. Poor prognostic characteristics such as host corneal stromal neovascularization, chronic intraocular inflammation, and increased intraocular pressure were not present before penetrating keratoplasty. Sugar and associates[13] demonstrated a continued rate of graft failure over time after penetrating keratoplasty for pseudophakic bullous keratopathy. They also documented a 28% decrease in donor endothelial cell density during the first year after penetrating keratoplasty in which a posterior chamber lens was retained.[13] With longer postoperative follow-up, our incidence of graft failure may increase.

The visual results reported in this series reflect visual acuity with spectacle as well as best corrected visual acuity. These values were different because of irregular astigmatism resulting from ocular surface abnormalities or retained corneal sutures. Although the post-keratoplasty corneal curvature, and therefore the refractive error, cannot be predicted accurately, no patient in this series had clinically significant anisometropia after surgery. Unless the posterior chamber lens implant is the incorrect power, dislocated, or causing recurrent hemorrhage or uveitis, it should not be replaced at the time of penetrating keratoplasty.

Previous studies have indicated the importance of primary endothelial disease in the development of pseudophakic bullous keratopathy after intracapsular cataract extraction. Arentsen and Laibson[14] found clinical evidence of endothelial dystrophy in 50% of contralateral eyes. Similarly, in contralateral eyes examined by specular microscopy, Waltman[6] found an average endothelial cell density of 1,850 cells/mm^2, despite little clinical evidence of endothelial disease. In this series, 11 of 13 (85%) nonoperated on contralateral eyes showed cor-

neal guttata or changes consistent with the diagnosis of Fuchs' dystrophy, an autosomal dominant disorder that affects women more severely than men.[15,16] The relatively rapid onset (average, eight months) of corneal edema in this group of elderly women suggests that primary endothelial dystrophy is an important predisposing factor in the development of pseudophakic bullous keratopathy after extracapsular cataract surgery. Other potential causes of endothelial cell loss such as chronic iritis, peripheral anterior synechiae, uncontrolled intraocular pressure, or dislocated intraocular lens implants were not noted in this series of patients before penetrating keratoplasty.

The surgical management of an eye with coexisting cataract and corneal endotheliopathy depends upon the functional status of the endothelium. Combined penetrating keratoplasty, extracapsular cataract extraction, and intraocular lens implantation (triple procedure) provides the most rapid visual rehabilitation of eyes with cataract and corneal edema. The latter may be suspected by a history of early morning blurring and confirmed by slit-lamp findings of microcystic epithelial edema, folds in Descemet's membrane, and abnormal corneal pachymetry measurements. In some cases, densely pigmented guttate plaques and a thickened Descemet's membrane may also cause visually significant corneal opacification in the absence of frank corneal edema and may necessitate combined penetrating keratoplasty and cataract extraction.

The surgical management of eyes with combined cataract and endothelial dystrophy without corneal edema is controversial. In most cases, such eyes would benefit from simple extracapsular cataract extraction with insertion of a posterior chamber lens implant. Penetrating keratoplasty may not be necessary, since dystrophic corneas may remain clear postoperatively despite decreased endothelial reserve. Simple extracapsular cataract extraction with posterior chamber intraocular lens implantation offers the best chance of rapid visual rehabilitation in this elderly age group, without the associated problems of penetrating keratoplasty such as delayed wound healing, astigmatism, and homograft rejection. Many of these patients are unable to handle contact lenses or have associated ocular surface or eyelid dysfunction and are poor candidates for aphakic contact lens wear. In addition, aphakic extended-wear lenses may induce corneal hypoxia and precipitate stromal edema in a marginally compensated cornea.[17] The placement of a posterior chamber lens implant using sodium hyaluronate poses a small risk to the corneal endothelium during cataract surgery and provides the patient with functional uncorrected vision.[18] In these patients, a mild reduction in postoperative visual acuity caused by corneal endothelial disease may be acceptable given the more rapid visual rehabilitation and lower complication rate of simple extracapsular cataract extraction and posterior chamber lens implantation. If corneal edema or opacification develops postoperatively, the prognosis for visual recovery after a subsequent penetrating keratoplasty remains excellent.

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OPHTHALMIC MINIATURE

The motions of the eye are effected by six muscles, which rise from the bone at the bottom of the socket and are fixed to the eyeball. Four of these are placed opposite to each other, and are called the *straight muscles*, one of which turns the eye upward and another downward; another turns it toward the nose, and the remaining one toward the temple. These muscles are named according to their actions. 'The upward turning of the eye' being expressive of devotion, the upper muscle is sometimes called *pius*, [the pious,] from producing this effect: it is also called *superbus*, [the proud,] because, with a peculiar disposition of the muscles of the face, it is partially elevated in pride. As a downward look is peculiar to modesty, the lower muscle is called *humilis*, [the humble.] The action of the muscle which draws the eye outward, causes the sideward looks that denote contempt, hence its name *indignabundus*, [the angry.] The muscle which draws the eye inward has its name *bibitorius*, [the drinker,] from directing the pupil to the bottom of the cup while drinking.

William Clay Wallace, *The Structure of the Eye. With Reference to Natural Theology*
New York, Wiley & Long, 1836, pp. 35 and 36

The Surgical Management of Overcorrection in Myopic Epikeratophakia

Bruce D. Nichols, M.D., F.R.C.S.(C.), Richard L. Lindstrom, M.D., and Alan V. Spigelman, M.D.

Three patients underwent myopic epikeratophakia that resulted in overcorrection. The surgical management of these cases involved resuturing the myopic lenticule to flatten the peripheral curvature and reduce the amount of minus power. A reduction in the overcorrection was achieved in all cases.

EPIKERATOPHAKIA was originally described as a surgical method to correct aphakia in adults.[1-5] Subsequently, the procedure has been used successfully in both myopia and keratoconus as a form of surgical management.[6-8] The problem of accuracy of correction has been especially evident in epikeratophakia for myopia and has resulted in lens design modifications and changes in surgical technique.

Herein we describe three cases of overcorrection in myopic epikeratophakia and present the surgical management and results of this technique.

Subjects and Methods

Three patients underwent epikeratophakia for myopia at our institution. The technique used was similar to that described elsewhere,[9] except that in each case the annular keratectomy was omitted. After suture removal and at a mean follow-up of six months, all patients were overcorrected (Table).

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All three patients underwent the same procedure in an outpatient operating room for surgical correction of their induced hyperopia. Retrobulbar and facial nerve blocks were administered and a sterile technique was used for the procedure. Terry keratometric readings were obtained from the corneal surface and compared with the most recent keratometry readings and manifest refraction values. The graft-host interface was identified and the epithelium was debrided for approximately 1 mm on each side for 360 degrees using a Tooke knife. Cocaine was not necessary. Copious irrigation removed the epithelial debris. The trephination groove and the peripheral corneal lamellar dissection plane were then fractured open anterior to the wing of the lenticule for the full circumference. We found that the best instrument for this was a Sinsky hook, as it was easily introduced into the correct plane and was of an appropriate width to separate the tissues. In most cases, the wing remained in the groove during the procedure and we did not find it necessary to lift it out to enhance the effect. Irrigation was then repeated. Eight interrupted 10-0 nylon sutures were then placed through the wing of the lenticule and exiting through the recipient in a fashion similar to the original suturing of the graft. A slip-knot technique was used, with all eight sutures left approximately 2 cm long and with just the first two throws in place to allow for adjusting. Terry keratometric readings were repeated. The tension of the sutures was adjusted to give the optimal amount of desired corneal steepening, trying to minimize any suture-induced astigmatism. The optimal amount of steepening was an amount at least equal in value to the magnitude of the overcorrection. For example, if the patient's keratometric reading was 40.00 diopters sphere and the patient was 5.0 diopters overcorrected, the sutures were tightened to give a reading of at least 45.00 diopters. Further steepening of 0.50 to 1.00 diopter was then

TABLE
VISUAL ACUITY AND SPHERICAL EQUIVALENTS

PATIENT NO., AGE (YRS), SEX	EYE	BEFORE EPIKERATOPHAKIA		AFTER EPIKERATOPHAKIA			AFTER RESUTURING			CHANGE IN SPHERICAL EQUIVALENT (D)
		BEST CORRECTED VISUAL ACUITY	SPHERICAL EQUIVALENT (D)	UNCORRECTED VISUAL ACUITY	BEST CORRECTED VISUAL ACUITY	SPHERICAL EQUIVALENT (D)	UNCORRECTED VISUAL ACUITY	BEST CORRECTED VISUAL ACUITY	SPHERICAL EQUIVALENT (D)	
1, 24, F	L	20/30−2	−12.75	20/400 (at 4 mos)	20/40+2	+9.37	20/60− (at 2 mos)	20/40+2	+1.12	8.25
2, 41, M	L	20/30−1	−8.62	20/60− (at 7 mos)	20/30	+2.25	20/30−1 (at 5 mos)	20/20+2	+0.37	1.87
3, 49, F	L	20/40−2	−16.62	20/80+2 (at 7 mos)	20/30	+5.25	20/40− (at 1.5 mos)	20/30−2	+0.75	4.50

performed so that further suture removal to augment the end result would be possible. Once the desired values were obtained, the last two throws were placed on each suture in a manner so as not to change its tension. The suture ends were cut short and the knots buried on the host side. Keratometric readings were repeated. If required, sutures were cut and replaced. Subconjunctival injections of gentamicin, cefazolin, and betamethasone were given. The eye was patched, a shield put in place, and the patient was examined the following day. Prophylactic topical antibiotics were used until full epithelialization had taken place. Sutures were only removed early if they were obviously loose. Manifest refraction and keratometric readings as well as keratoscopy were used to measure the patient's progress and further suture removal was performed on a case-by-case basis.

Results

None of the patients had a preoperative best corrected visual acuity of 20/25 or better and all were severely myopic (Table). The average postepikeratophakia spherical equivalent was +5.62 diopters at a mean follow-up time of six months; uncorrected visual acuity ranged from 20/60− to 20/400. Best corrected visual acuity after resuturing remained generally unchanged from the postepikeratophakia best corrected visual acuity. The postresuturing uncorrected visual acuity, however, improved dramatically in each patient (Table). The average spherical equivalent after restructuring was +0.75 diopters (range, +0.37 to +1.12 diopters), with a mean follow-up period of 2.8 months. The average change in spherical equivalent for the three patients was 4.87 diopters after resuturing.

Discussion

Variable refractive results are possible with myopic epikeratophakia. Because the epikeratophakia lenticule relies on the shoulder of the button to effect its minus power and because this is in the area where the suturing is taking place, there can be much suture-to-suture and surgeon-to-surgeon variability.[6] A tight suture would cause the shoulder to flatten and thus reduce the minus power; conversely, a loose suture would allow the shoulder to ride up and increase the minus power.

There may also be inconsistency in creating a uniform annular keratectomy. Wide keratectomies can cause an undercorrection as the shoulder falls into the area and thus, it cannot exert its refractive effect. Similarly, an irregular keratectomy can result in astigmatism.[6] In an attempt to eliminate this variable, the annular keratectomy has been omitted in all of our myopic and aphakic epikeratophakia procedures. This, however, has introduced another variable in the procedure: the expected power from a given lenticule. The peripheral curvature relationships are altered without the keratectomy and, accordingly, the final refractive result will be affected. The shoulder of the button will ride higher without the keratectomy, which will give more minus power in the

myopic procedures for a net overcorrection; however, this should be uniform around the circumference of the lenticule and no astigmatism should be induced. Similarly, in the aphakic cases the absence of the keratectomy will effectively flatten the peripheral curves, giving less plus power for a net undercorrection.

In our three cases, the amount of overcorrection was visually significant. All of the patients were dissatisfied with their postepikeratophakia uncorrected visual acuity. It is unlikely that any one factor was responsible for the entire magnitude of the overcorrection, as other similarly performed procedures (without a keratectomy) have not resulted in such large refractive errors. The technique used to resuture these lenticules effectively steepened the central cornea in each case and reduced the amount of overcorrection. The mean postresuturing spherical equivalent of +0.75 diopters illustrates the vast improvement from the preresuturing value of +5.62 diopters. All three eyes are within 1.25 diopters of plano and all are symptomatically improved with respect to their postresuturing uncorrected visual acuity. Both Patients 2 and 3 have a postresuturing best corrected visual acuity that is better than their best corrected visual acuity before undergoing epikeratophakia. Patient 1 had the greatest amount of overcorrection, which was demonstrated by the largest change in spherical equivalent from the resuturing and the largest residual hyperopia after two months of follow-up. Placing more than eight sutures might have decreased the spherical equivalents further by causing additional central corneal steepening. Ideally, as in Patient 2, selective suture removal will reduce both astigmatism and residual myopia to bring the refractive error toward plano.

These cases demonstrate that the surgical management of overcorrection in myopic epikeratophakia can result in lessening of the induced hyperopia and allow for symptomatic improvement. The future of epikeratophakia for myopia relies on overcoming some of the inconsistencies and making the procedure more reproducible. Newer technology with nonfreeze tissue processing and perhaps the elimination of sutures with the use of biodegradable wound glues[6] may make the procedure more consistent and predictable.

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The Risk of Cytomegalovirus Transmission by Penetrating Keratoplasty

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To investigate the risk of cytomegalovirus transmission by corneal transplantation, we quantitated anticytomegalovirus IgG levels of donor, preoperative, and postoperative serum samples. Of 118 patients, 79 (67%) were seropositive preoperatively. Twenty-five patients who were seronegative preoperatively received a graft from a positive donor and two (8%) seroconverted. Eleven patients who were seronegative preoperatively received a graft from a negative donor and one (9%) seroconverted. None of the patients who seroconverted had a febrile illness and all three grafts were clear.

PENETRATING KERATOPLASTY is the most common type of organ tissue transplantation in the United States, with over 30,000 performed in 1985.[1] Although it is a safe and effective procedure, corneal tissue can, on rare occasion, transmit such infections as rabies[2-4] and Creutzfeldt-Jakob[5] disease. Because of the risk of transmission of disease by corneal tissue, the Eye Bank Association of America presently recommends that serologic testing for hepatitis B and human immunodeficiency virus infection be performed on all donors (Medical standards, Eye Bank Association of America, July 1, 1987). It also recommends rejecting all potential donors with neurologic or neoplastic disease of unknown or viral origin.

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Cytomegalovirus infection is a common cause of serious illness and death after major organ transplantation (other than cornea).[6,7] Cytomegalovirus is a virus of the herpes family. Infection with cytomegalovirus in the general population is common, with 50% to 100% of adults having antibody indicative of previous infection.[7] The incidence of positive serologic results increase with age. A person with normal immunity who is infected is often asymptomatic. If symptoms are present, the most common manifestation is fever. After an acute infection, a long-lived latent infection, which may reactivate or transmit the disease, can occur.[7] The virus may remain latent in lymphocytes.[8]

Cytomegalovirus may be transmitted from an asymptomatic seropositive donor to another individual by kidney, heart, liver, or bone marrow transplantation as well as by blood transfusion.[6,9,10] In contrast to a person with normal immunity, a cytomegalovirus infection in an immunocompromised patient is much more likely to result in clinical disease. The clinical manifestations of a cytomegalovirus infection include cytomegalovirus mononucleosis syndrome, retinitis, pneumonitis, hepatitis, encephalitis, disseminated infection, and death.[7] A major risk factor for new cytomegalovirus infection in organ recipients is the serologic status of the donor.[6,10]

Whether cytomegalovirus can be transmitted by corneal tissue has not, to our knowledge, been studied. Although the cornea is largely avascular, lymphocytes and other cells that have hematopoietic cell markers are present in the central cornea.[11,12] Cytomegalovirus can be isolated from tears[13] and appears to have an affinity for ocular and neurologic tissue, as shown by the common finding of cytomegalovirus retinitis in patients with the acquired immune deficiency syndrome. It is possible, therefore, that the cornea could transmit the virus.

Most patients who undergo penetrating kera-

toplasty do not receive systemic immunosuppressive drugs, and therefore if infection occurred it would probably not be clinically significant. However, some patients who undergo corneal transplantation are receiving immunosuppressive drugs for other conditions, such as rheumatoid arthritis or cancer. Others who might be severely affected by cytomegalovirus infection include pregnant women, since primary infection during pregnancy can lead to severe disease in the developing infant.[7]

In many institutions all major organ donors are routinely screened for antibodies to cytomegalovirus. Since many organ donors are also corneal tissue donors, results of serologic testing for cytomegalovirus may already be available. Presently, this information is ignored, since data as to its potential importance are lacking.

We performed a serologic study of donors and recipients of corneal tissue to investigate whether cytomegalovirus can be transmitted by penetrating keratoplasty and to explore the need for routine screening of donors and recipients of corneal tissue for cytomegalovirus infection. Cytomegalovirus is a lymphotrophic and neurotrophic virus that may cause a long-lived infection that can be transmitted by organ donation and blood transfusion. In these characteristics it is similar to the human immunodeficiency virus. Information about cytomegalovirus transmission might be useful in investigating whether AIDS could be transmitted by corneal transplantation.

Material and Methods

After informed consent, paired blood samples were obtained from recipients of corneal tissue at their preoperative visit and at least three months postoperatively. The residual serum from samples collected from donors for routine hepatitis B surface antigen and human immunodeficiency virus testing was also saved. All serum samples were frozen at −75 C before antibody testing. IgG anticytomegalovirus assays were performed by the enzyme immunoassay method. Corrected absorbance values of greater than or equal to 0.25 were considered positive for IgG anticytomegalovirus. Known positive and negative controls were included in the test run and selected positives were confirmed by immunofluorescence assay using cytomegalovirus-infected fibroblast substrate. All spectrophotometric measurements were performed at 405 nm by an automatic plate reader. The difference between the absorbance value of the serum's antigenic reaction and the serum's control reaction was calculated and plotted against a calibration curve constructed from three calibrator specimens. The result gave the corrected absorbance value. Using the absorbance results to determine the significant increase in antibody titers involves the calculation of a critical ratio. The critical ratio is determined by dividing the mean absorbance value of the convalescent serum by the value of the acute serum. If this value is less than 1.47, it is interpreted as being no significant change in antibody level. A value of 1.47 to 1.64 is suggestive of significant rise in antibody comparable in significance to a fourfold increase in antibody titer. A value of greater than 1.65 is indicative of a highly significant rise in cytomegalovirus-specific antibody comparable to greater than a fourfold increase in antibody titer.

At the time the postoperative sample was drawn, all patients answered questions concerning the presence of febrile illness or any recent blood transfusions. All charts were reviewed for medical problems including any immunosuppressant regimen and the outcome of the transplant.

Serum samples were collected from a total of 118 patients. After none of 43 patients who were seropositive preoperatively showed a significant rise in titer, it was elected to stop drawing the postoperative sample on patients who were seropositive preoperatively. However, we continued to collect postoperative samples on all patients who were seronegative before transplantation. A total of 39 patients were identified to be seronegative preoperatively and postoperative samples were obtained on 36. Of the three patients in whom samples were not collected, one patient moved out of the area before three months and in two no sample was obtained at their postoperative visits.

Results

The incidence of antibody to cytomegalovirus in our donor population was 62% and in the recipient population was 67%. The average age of the seropositive recipients was 68 years and of the seronegative recipients was 45 years.

This difference was statistically significant ($P < .0001$). Reflecting the age difference, the most common diagnosis in the positive recipients was aphakic or pseudophakic bullous keratopathy and the most common diagnosis in the negative recipients was keratoconus. Of the 43 patients who were seropositive preoperatively, 25 received a graft from a seropositive donor and 15 received a graft from a seronegative donor. None of these patients showed a significant rise in titer. One patient in each group had a suggestive increase in titer. Because none of these first 43 recipients who where seropositive preoperatively showed a significant rise in antibody levels, we assumed that such a rise was rare and stopped collecting postoperative specimens in this group.

Twenty-five patients who were negative preoperatively for antibodies received a graft from a seropositive donor. Two of these patients (8%) converted. Eleven patients who were seronegative preoperatively received a graft from a seropositive donor. One of these (9%) also seroconverted (Table). Of the three patients who converted, none had a blood transfusion or febrile illness in the perioperative period. None of the three were immunocompromised. All three of the grafts were clear at the most recent visit.

One patient who was seronegative preoperatively and received a graft from a positive donor was immunocompromised. He had received multiple doses of chemotherapy and radiation therapy for systemic lymphoma. He did not seroconvert.

TABLE
INCIDENCE OF SIGNIFICANT RISE IN CYTOMEGALOVIRUS TITER AFTER PENETRATING KERATOPLASTY
(N = 118)

CYTOMEGALOVIRUS STATUS OF DONOR/RECIPIENT	NO. OF PATIENTS	NO. OF PATIENTS TESTED POSTOPERATIVELY	NO. OF PATIENTS WITH POSTOPERATIVE RISE IN CYTOMEGALOVIRUS TITER	
			NO.	(%)
Positive/positive	45	28*	0	(0)
Negative/positive	34	15*	0	(0)
Positive/negative	28	25	2	(8)
Negative/negative	11	11	1	(9)

*Because the first 43 seropositive recipients did not have a significant rise in the cytomegalovirus titer, the postoperative specimen collection was discontinued.

Discussion

In kidney or heart transplantation, a major source of cytomegalovirus infection is the donor organ. The risk of cytomegalovirus infection after transplantation is 60% to 100% for a negative recipient receiving a positive graft.[6,14-16] It has therefore been recommended that all patients and donors be screened by cytomegalovirus serologic testing preoperatively to avoid causing cytomegalovirus infection by giving a positive organ to a negative recipient.[9] The risk in corneal transplantation is much lower. None of 43 seropositive patients showed evidence of new infection. In the seronegative individuals studied, over 90% remained seronegative after the operation. Those patients who seroconverted demonstrated no clinical symptoms. There was no difference in the rate of seroconversion between patients who received a positive graft and those who received a negative graft. Therefore, it does not seem worthwhile to obtain cytomegalovirus serologic test results on the routine patient before undergoing penetrating keratoplasty.

A more difficult question is whether cytomegalovirus can be transmitted by penetrating keratoplasty and whether immunocompromised or pregnant patients should be screened preoperatively. Our evidence, while not conclusive, is against transmission of cytomegalovirus by corneal tissue. There was no difference in the rate of seroconversion between patients who received a positive and a negative graft, but only one person who received a negative graft seroconverted. This could have been caused by an unrelated exposure to the virus or a lack of sensitivity in the assay of the donor specimen to demonstrate antibodies and possible infectivity. The rate of seroconversion associated with organ transplantation when a negative recipient receives a positive organ is between 60% and 100%. This is certainly much higher than the 9% found in our study. The rate associated with blood transfusions is 13% to 24%[6] and also appears higher than that found in our study. However, our rate of perioperative seroconversion appears higher than the approximately 2% per year background rate found in people exposed to a hospital environment.[17] Our sample size is too small to detect

confidently a difference between a roughly 10% perioperative seroconversion rate and the expected background seroconversion rate of approximately 2% per year.

The power of our study to detect this difference is 0.29, using a one-sided proportion test. Such a study would need to examine roughly 190 seronegative patients or screen roughly 570 total patients to achieve a power of 0.80. Therefore, we cannot conclusively say that cytomegalovirus cannot be transmitted by corneal tissue, but the risk of transmission appears to be low. Routine screening for antibodies to cytomegalovirus for nonimmunocompromised corneal tranplant recipients does not appear to be indicated. However, a study of the risks of transmission in immunocompromised patients undergoing corneal transplantation may be warranted.

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Microbial Keratitis Associated With Contaminated Ocular Medications

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We studied seven cases of severe gram-negative microbial keratitis associated with the use of contaminated topical ocular medications. Five cases involved *Pseudomonas aeruginosa*, one involved *Serratia marcescens*, and one involved *Proteus mirabilis*. In each case the same organism was cultured from corneal scrapings and from the medication. Either prednisolone acetate (one case) or timolol maleate (seven cases) was implicated in all instances.

CHRONIC OCULAR SURFACE disruptions pose a significant potential risk for the development of bacterial keratitis. The stage is set for infection by recurrent or persistent epithelial breaks that presumably allow inocula of pathogenic organisms to become established in the underlying stroma.

Microbial keratitis occurring in eyes that have undergone surgery or have chronic ocular surface disease is typically associated with gram-positive organisms, particularly staphylococci and streptococci.[1] However, gram-negative keratitis is also recognized to occur in the same clinical settings. The source of the gram-positive infections is presumed to be indigenous conjunctival and ocular adnexal flora, but the origin of the gram-negative infections is usually not evident. We studied seven cases of severe gram-negative microbial keratitis in eyes with preexisting ocular surface abnormality. In each case the same organism was cultured from both the cornea and an in-use topical ocular medication. Antibiotic sensitivities by Kirby-Bauer disk testing were identical for all corneal and medication isolates.

Case Reports

Case 1

A 75-year-old woman with a history of angle-closure glaucoma and subsequent advanced cataract and corneal edema in the left eye had marked periorbital edema, diffuse corneal ulceration with purulent discharge, and a 25% hypopyon. The cornea and medications used (timolol maleate 0.5% and pilocarpine 2%) were cultured, and intensive antibiotic treatment was begun. Cultures of the cornea and of the timolol maleate, the latter dropped directly from the bottle onto blood agar, grew abundant *Pseudomonas aeruginosa*; the pilocarpine culture was negative. Despite the intensive use of antibiotics to which the organism was sensitive, the infection spread to the sclera, and the eye was eventually enucleated.

Case 2

An 81-year-old man with a history of bullous keratopathy and secondary glaucoma in the left eye four years after intracapsular cataract extraction and implantation of a closed-loop anterior chamber intraocular lens had an extensive inferocentral stromal infiltrate, with an overlying epithelial defect (Fig. 1). Cultures were taken of the corneal infiltrate and the patient's timolol maleate 0.5% and prednisolone acetate 1%, and intensive broad-spectrum topical antibiotic treatment was begun. Cultures from the cornea and from the timolol maleate, the latter dropped directly from the bottle onto blood agar, grew abundant *P. aeruginosa*; the prednisolone culture was negative. Antibiotic treat-

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Fig. 1 (Schein and associates). Case 2. *Pseudomonas aeruginosa* corneal ulcer in setting of pseudophakic bullous keratopathy.

ment for two weeks resolved the infiltrate and the epithelial defect. Two months later a penetrating keratoplasty and intraocular lens exchange were performed without complication.

Case 3

A 73-year-old man with a long and complicated ocular history that included aphakic bullous keratopathy, chronic blepharitis, and multiple penetrating keratoplasties in both eyes had a corneal stromal infiltrate in the graft in the right eye. Current ocular medications were timolol maleate 0.5% twice daily, prednisolone acetate 1% once a day, and bacitracin ointment once a day. Cultures from the cornea and the timolol maleate, the latter dropped directly onto blood agar, grew *P. aeruginosa*. Outpatient treatment resulted in resolution of the infection and a central scar.

Case 4

A 75-year-old woman inflicted a corneal abrasion on her left eye with a mascara brush (previously reported[2]). She was treated initially with erythromycin ointment. Four days later she had decreased vision, extensive ulceration of the inferior cornea, and a hypopyon in the same eye. The cornea, conjunctiva, mascara, mascara brush, and the inner part of the cap and eyedropper tip of the patient's bottle of timolol maleate 0.5% were cultured. Cultures of the cornea and of the inside of the timolol bottle cap grew *P. aeruginosa*; all other cultures were negative. The patient was hospitalized for 12 days of intensive antibiotic therapy. On discharge a large central scar was noted. Thirty-nine days after discharge, recurrent *P. aeruginosa* keratitis developed and spread to adjacent sclera. The infection was controlled but resulted in a diffusely scarred cornea and a painful eye requiring retrobulbar alcohol for relief.

Case 5

An 87-year-old woman with a history of open-angle glaucoma, treated for ten years with timolol maleate 0.5% in both eyes once a day, underwent a routine examination by her local ophthalmologist. The findings were normal except for cataract, and plans were made for elective cataract extraction from the left eye. On examination ten days later she had an extensive corneal infiltrate (Fig. 2). Corneal scrapings grew *P. aeruginosa* as did swab cultures of the timolol maleate bottle tip and cap. The contents of the bottle extracted under sterile conditions were passed over a Millipore filter, which was then placed directly onto sheep blood agar. This culture also yielded *P. aeruginosa*. The patient stated that the current 10-ml bottle of timolol maleate had been in use for approximately eight weeks and was stored in the bathroom. She was hospitalized for ten



Fig. 2 (Schein and associates). Case 5. *Pseudomonas aeruginosa* corneal ulcer after ocular examination.

days. On discharge an extensive central corneal scar was noted.

Case 6

Eighteen months after penetrating keratoplasty for pseudophakic bullous keratopathy in an 84-year-old woman, the running suture was removed. On examination five days later she had a corneal stromal infiltrate at the wound margin. Cultures from the cornea and the patient's timolol maleate, the latter dropped directly onto blood agar, grew *Serratia marcescens*. A culture of prednisolone acetate was sterile. The patient responded to antibiotic treatment, and moderate wound slippage, without perforation or graft failure, resulted from the infection.

Case 7

A 67-year-old man with a history of aphakic bullous keratopathy had a large central corneal stromal infiltrate. Cultures from the cornea grew *Streptococcus pneumoniae* and *Proteus mirabilis*. Cultures from in-use timolol maleate, dropped directly onto blood agar, grew *P. mirabilis*. Cultures from the prednisolone acetate used by the patient, dropped directly onto blood agar, grew *P. mirabilis* and *S. marcescens*. The three *Proteus* growths showed identical antibiotic sensitivities on Kirby-Bauer disk testing. Inpatient treatment resulted in resolution of the infection and a dense central corneal scar.

Discussion

In each case described, the same gram-negative organisms were cultured from both the cornea and the topical medicine. Templeton and associates[3] described three cases of *S. marcescens* keratitis after keratoplasty, two of which occurred at the graft-host junction. In all three cases, the organism was recovered from either the dead space in the eyedropper cap or the grooves of the bottle tops of prednisolone sodium phosphate or timolol maleate. The organism was cultured from the eyedropper once, and solutions cultured directly from the bottles were all sterile.

To our knowledge, the cases reported here represent the first series in which *P. aeruginosa* appeared to cause suppurative keratitis by direct inoculation from topical medicines. Unfortunately, we did not culture all possible sources of contamination in all of the cases. In Cases 1, 2, 3, 6, and 7, the cultures were limited to a specimen taken by simple inversion of the bottle to allow a drop to fall onto blood agar so that we cannot identify whether contamination occurred within the bottle itself, the tip, or the cap. However, the method of taking the cultures in these cases mirrors the method of self-administration of the medication by the patient. In Case 4, the contamination was found to be limited to the inside of the bottle cap. In Case 5, *P. aeruginosa* was isolated from all sources cultured, including the interior of the bottle. The potential value of culturing topical ocular solutions by passing the entire contents over a Millipore filter is raised by this case, the only one in which this procedure was used.

The reported findings on contamination of topical ocular medications are inconsistent. Høvding and Sjursen[4] found bacterial growth by drop culture in 82 (12.9%) of 638 multidose eyedrop bottles. Swabbings from 180 dropper tips yielded bacteria in 38 (21.1%); none of the pipette aspirates from 196 bottles were positive. Contamination did not increase with duration of use of the bottles. The bacteria isolated were predominantly coagulase-negative staphylococci and micrococci, and no significant difference was found between organisms isolated by dripping and by tip swabbing. No gram-negative organisms typically associated with bacterial keratitis were isolated. The findings argue for the sterile milieu of the interior of topical medications, but may be limited in their wider applicability, since only 19% of the bottles were used by outpatients; the remainder were used by physicians in examination rooms or delivered by nursing staff to inpatients.

Marion and Tapert[5] examined bacterial contamination in timolol maleate bottles in use by a nonselected clinic population and found growth from drop cultures in 16 of 51 bottles (31.4%). In addition to normal skin flora, they isolated *P. mirabilis*, *S. marcescens*, *Morganella morganii*, and *Candida parapsilosis*. The bottle tip alone was the bacterial source in two of the 16 bottles (12.5%). Solution that had been extracted in a sterile manner and the bottle tip were contaminated in ten of the 16 bottles (62.5%). In this study, the degree of contamination increased with time since the filling of the prescription.

In conjunction with Marion and Tapert's report,[5] we find our clinical cases a source of

concern. Six of our seven patients were examined over a one-year period. However, the real frequency is certainly larger, since cultures of topical medications have heretofore not been routinely performed in a standardized fashion. It is conceivable, although unlikely, that the contamination of the topical medications with *Pseudomonas*, *Serratia*, and *Proteus* could have derived primarily from a previously infected cornea, with secondary contamination of the bottle. However, gram-negative colonization in normal conjunctival flora is rare and pseudomonal colonization appears to be on the order of 1% or less.[6-8] *Serratia* and *Proteus* are even more unusual in this setting. There are also several clear precedents for exogenous inocula of gram-negative organisms with resultant suppurative keratitis. Most importantly, contact lens care solutions contaminated with *P. aeruginosa* have been strongly implicated in the development of contact lens-associated microbial keratitis.[9-11] Identical physiologic properties, antibiograms, serotypes, and plasmid profiles have been described for *P. aeruginosa* isolated from corneal ulcers and from in-use saline solutions.[11] Exogenous infection of the cornea with *P. aeruginosa* has also been noted in association with contaminated eye cosmetics and applicators.[12-14] Finally, Cases 4, 5, and 6 are each notable for a specific event in which the surface epithelium was disrupted (mascara abrasion, applanation, suture removal) at a time when the cornea was known to be free of infection. In these three cases, suppurative keratitis and contaminated ocular medications were discovered within ten days of the inciting event.

We have no reason to believe that timolol maleate has a particular susceptibility to contamination. The case reports may simply reflect the frequency of use of this medication. However, these cases raise two issues of more general concern and interest: the source of gram-negative organisms, particularly *Pseudomonas;* and the steps necessary to prevent contamination. Under normal circumstances, *Serratia* and *Pseudomonas* species are rare fecal or skin contaminants. Both organisms are frequently found in foodstuffs and kitchen items, and *Pseudomonas* has been cultured repeatedly from water supplies and faucet aerators.[15-17] Further investigation into home sources of gram-negative colonization may also be informative about the origins of pseudomonal keratitis associated with soft contact lens wear, a problem of far greater proportions.

Solutions to the problem of microbial contamination of topical medications and contact lens care products will probably require not only technologic modifications but also patient education and responsibility. In a laboratory study examining the potential contamination of a fluorescein-anesthetic combination with *P. aeruginosa*,[18] bacterial growth was found in the caps of multidose squeeze bottles, but the caps of pipette bottles self-sterilized rapidly after inoculation. The authors concluded that the use of a pipette-type dispenser decreases the risk of microbial contamination and growth, at least under laboratory conditions.

The relative contribution of patient behavior to product contamination also merits further attention. For example, it may be significant that Patient 5 stored her bottle of timolol maleate in the bathroom, or that one bottle lasted so long because of once-daily usage. We are currently investigating the role of patient habits, methods of self-delivery, and storage sites of topical medications in an effort to develop preventive strategies. In the interim, we recommend culture of all topical medications, as well as of contact lens-related products, whenever the cornea is cultured for suspected microbial keratitis. These culture results may be helpful beyond the stage of initial treatment. They may highlight faulty techniques of medication or contact lens use that put the patient at continued risk.

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OPHTHALMIC MINIATURE

"Have a care there, Mr. MacMahon. If irony is to be employed in these proceedings, you will entrust it to me. You did not offer the oath to your scholars, but the oath was taken by young men who had been your pupils in earlier years. Mark that I say 'was taken': the passive voice is to be avoided in literature, but it is useful in law. . . ."

Thomas Flanagan, *The Tenants of Time*
New York, E. P. Dutton, 1988, p. 238

Ocular Involvement in Mycotic Sinusitis Caused by *Bipolaris*

Walter M. Jay, M.D., Robert W. Bradsher, M.D., Brad LeMay, M.D., Nancy Snyderman, M.D., and Edgardo J. Angtuaco, M.D.

We examined two patients with unilateral ophthalmologic findings secondary to pansinusitis caused by *Bipolaris*. Both patients were healthy young men. One patient had a gradual visual loss, whereas the other showed proptosis. Surgical debridement was the primary treatment in both patients. One patient received antifungal therapy, whereas the other was cured with surgery alone.

FUNGI can be subdivided into yeasts and molds. Yeastlike fungi are round or oval and reproduce by budding. Molds are composed of hyphae, which are tubular. Molds grow by branching and longitudinal extension. Some fungi can grow either as a yeast or as a mold. Although there are many ways to classify fungi, one way involves an organism's typical appearance in tissue.[1] Examples of yeastlike fungi include *Histoplasma capsulatum*, *Candida albicans*, and *Cryptococcus neoformans*. Examples of molds include *Aspergillus*, *Mucor*, and *Bipolaris*.

Bipolaris, a dematiaceous septate fungus, is found in dust, soil, and decaying matter. Recently, cases of pansinusitis and other infections caused by dematiaceous fungi have been reported in healthy young patients.[2-6] The taxonomy of these organisms has been confusing because of recent changes in classification. We studied two cases of unilateral ophthalmologic changes secondary to *Bipolaris* pansinusitis, and focus herein on the radiographic changes and the taxonomic classification of these organisms.

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Case Reports

Case 1

An 18-year-old man was referred to the Neuro-ophthalmology Service of our institution with a two-month history of gradual, progressive visual loss in his right eye. His medical history was remarkable for inhalant allergies and previous sinus surgery involving maxillary sinus nasal-antral windows. For the previous six months, he had suffered nasal stuffiness, mucoid rhinorrhea, and midfacial headaches.

On examination, best corrected visual acuity was R.E.: 20/400 and L.E.: 20/20. The right pupil was sluggish, with a right afferent pupillary defect. On Hardy-Rand-Rittler color plate testing, the patient correctly answered zero of ten in the right eye and ten of ten in the left eye. A Goldmann visual field showed a right central scotoma. Ophthalmoscopic examination was normal.

Magnetic resonance imaging disclosed masses in the paranasal sinuses and nasal cavities (Fig. 1). On coronal T_2-weighted images, there was extension of the mass into the right anterior clinoid process (Fig. 2). The central portion of the mass in the sphenoid sinus had a diminished signal intensity on T_1- and T_2-weighted sequences, whereas its rim showed an increased signal on a T_2-weighted sequence. Based on the clinical findings and magnetic resonance imaging study, bilateral ethmoidectomies, Caldwell-Luc procedures, and sphenoidectomies were performed. Results of biopsy showed distorted fusoidal hyphae (Fig. 3) and the cultures demonstrated *Bipolaris spicifera*. Postoperatively, the patient received the oral, imidazole antifungal agent itraconazole.

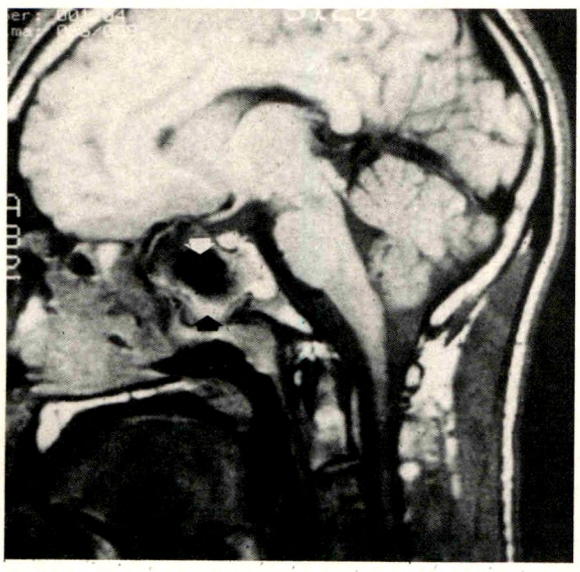


Fig. 1 (Jay and associates). Case 1. Midline sagittal magnetic resonance imaging scan, T_1-weighted (repetition time, 600 msec; echo time, 20 msec) shows a mass in the sphenoid sinus with a central area of diminished (white arrow) signal intensity surrounded by a slightly hyperintense rim (black arrow).

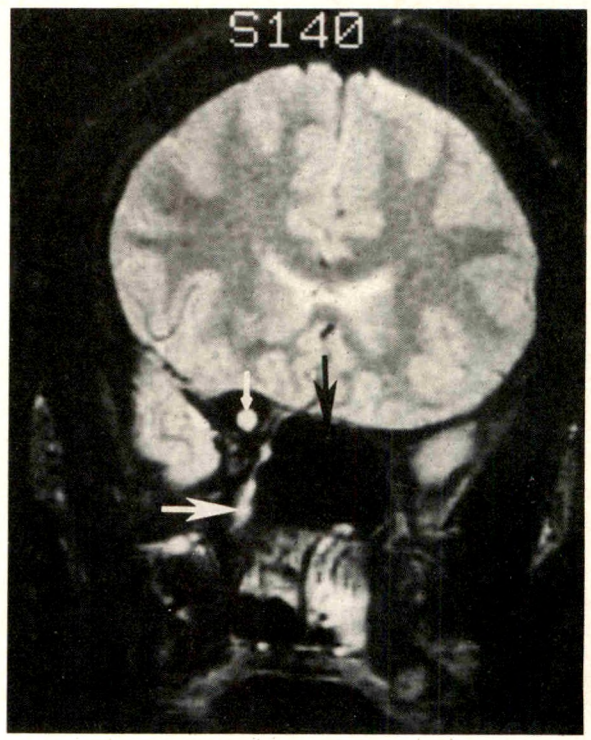


Fig. 2 (Jay and associates). Case 1. T_2-weighted coronal magnetic resonance imaging scan (repetition time, 2,000 msec; echo time, 80 msec) through the sphenoid sinus shows extension of the abnormality into the right anterior clinoid process, with a central area of hyperintensity (small white arrow) surrounded by a dark rim. The abnormality in the sphenoid sinus demonstrates no change in the central area of diminished signal intensity (black arrow), whereas its peripheral rim shows increase in signal (large white arrow).

A subsequent noncontrast computed tomographic scan showed soft tissue of high attenuation in the paranasal sinuses. In the sphenoid sinus, the abnormality extended and eroded into the right anterior clinoid process (Fig. 4). Pansinusectomy and right optic nerve decompression were performed via external ethmoidectomy. Postoperatively, the patient received a 600-mg course of intravenous amphotericin B.

Two months after the initial examination, visual acuity in the right eye was counting fingers at 1 foot. Visual acuity in the left eye remained 20/20. Ophthalmoscopy showed disk pallor in the right eye. A repeat computed tomographic scan demonstrated marked resolution of the abnormality in the sphenoid sinus and right anterior clinoid process (Fig. 5). He continued to take oral itraconazole for one year.

Case 2

This 17-year-old boy had intermittent nasal obstruction with increasing rhinorrhea for one year. For the preceding month, his family had noted increasing proptosis. He denied any history of chronic sinusitis. On examination right proptosis and a pale, multilobulated, polypoid mass filling the nasal cavity on the right side were noted. Computed tomography demonstrated a mass in the ethmoid and sphenoid sinuses, which expanded into the medial aspect of the right orbit (Fig. 6). No bony or intracranial invasion was noted. An ethmoidectomy, sphenoidectomy, and a right Caldwell-Luc procedure were performed. Results of biopsy showed broad, septate hyphae, and *Bipolaris spicifera* was isolated by culture. One month later, a repeat drainage procedure was required for recurrence of a polypoid lesion. Culture of the surgical material grew both *Curvularia lunata* and *Bipolaris spicifera*. No antifungal therapy was given. The proptosis resolved postoperatively and no recurrences have been noted for two years after the surgical procedure.

Mycology methods

Surgical specimens were maintained aseptically until inoculated onto agar culture media.

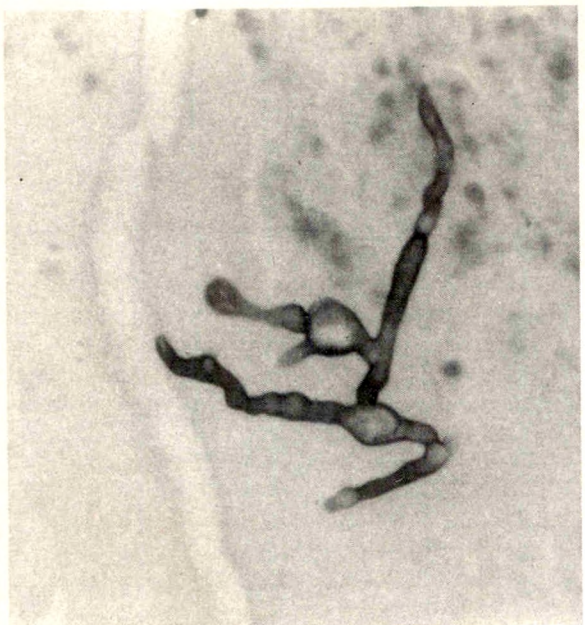


Fig. 3 (Jay and associates). Case 1. Section of intrasinus mass showing hyphae (Gomori methenamine-silver, ×800).

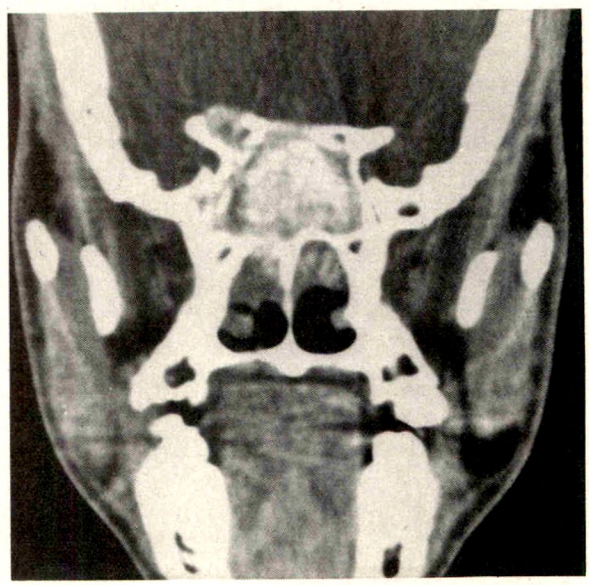


Fig. 4 (Jay and associates). Case 1. Noncontrast computed tomographic scan through the anterior clinoid process shows a central hyperdense mass in the sphenoid sinus, which extends and erodes the right anterior clinoid process.

Specimens were plated onto Sabouraud's agar supplemented with gentamicin and onto brain-heart infusion agar supplemented with cycloheximide, gentamicin, and chloramphenicol. Plates were incubated at 25 C in room air and observed daily for growth for seven days. Fungal colonies were velvety, gray-black, and flat on the surface. Portions of the colonies were removed and viewed microscopically with lactophenol cotton blue preparations. Oblong, fusoidal-shaped fungi were examined further. Particular attention was paid to the conidial shape, presence of a protruding hilum, and the contour of the basal portion of the conidia.

Discussion

Two forms of ocular involvement as a result of mycotic sinusitis have been described.[5] The more widely recognized has been the aggressive form in immunocompromised patients, with rapid destruction of host tissues. Fungi that cause such acute disease include *Mucor* and *Fusarium*. The second form is more chronic and ranges from colonization to mycetoma to tissue invasion. A wide range of fungi have been described with this form, including the organisms causing phaeohyphomycosis. Phaeohyphomycosis refers to an infection caused by dematiaceous, or darkly pigmented, environmental fungi called Hyphomycetes, of which there are 30 different species.[2,4-9] These

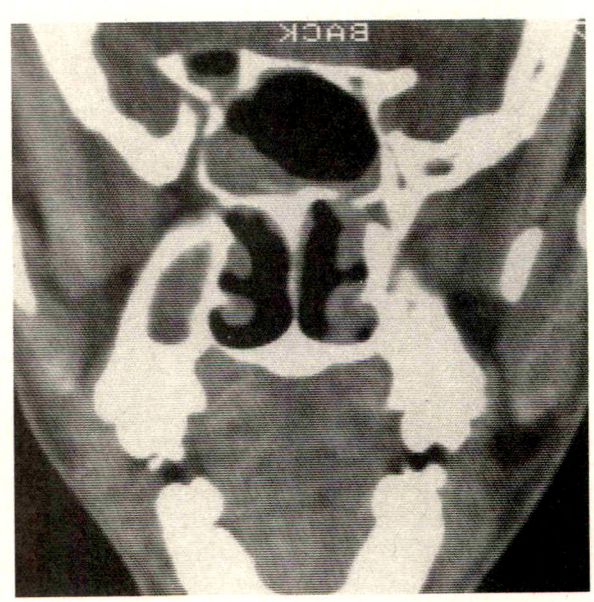


Fig. 5 (Jay and associates). Case 1. Postoperative noncontrast computed tomographic scan demonstrates marked resolution of the abnormality in the sphenoid sinus and right anterior clinoid process.

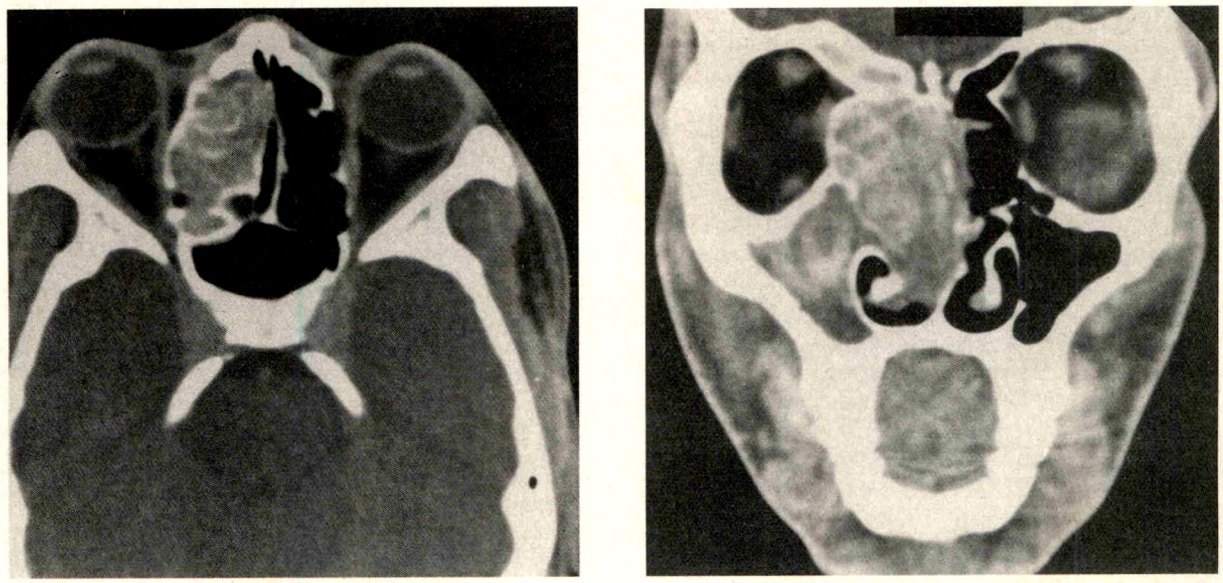


Fig. 6 (Jay and associates). Case 2. Left, Axial computed tomographic scan demonstrates a high-density expansile mass in the right ethmoid sinuses, causing proptosis of the right globe. Right, Coronal computed tomographic scan shows extension of the abnormality into the right nasal cavity and maxillary sinus.

organisms have been reported to cause disease in a variety of organs including cutaneous, pulmonary, osseous, peritoneal, cardiac, central nervous system, and ocular tissues.[4,5]

The less aggressive form of mycotic sinusitis is found in previously healthy persons. Both cases we report occurred in healthy young men without previous systemic illness. Although an occupational exposure has not been reported in each case, both of our patients were high school football players. Rohwedder and associates[6] and Brummund and associates[5] have previously reported this epidemiologic clue in two patients with phaeohyphomycosis. Swimming and cutaneous trauma have also been associated with this mycotic infection.[7,9,10] A common feature in cases of sinusitis caused by *Hyphomycetes* is a history of allergic rhinitis.[2,3,5,9,11] During sinus surgery, chronic eosinophilic infiltration has been described. The diagnosis of this fungal infection is made by histopathologic identification of the organism in the intracavitary necrotic mass. Patients with chronic sinusitis after a history of allergic rhinitis and nasal polyposis may have phaeohyphomycosis of the sinuses.

The organism responsible for infection in our two patients has been identified in previous reports as *Helminthosporium spicifera*, *Brachcladium spicifera*, and *Curvularia spicifera*, but most cases have been described as *Drechslera spicifera*. Although Shoemaker[12] proposed the name *Bipolaris* in 1959, these fusoid or globoid conidia with germination only from the end cells have only recently been referred to by this name, as recommended by McGinnis, Rinaldi, and Winn[8] and by Adam and associates.[9] The specific mycologic techniques and points that separate these organisms have been extensively reviewed.[8,9] We agree that *Bipolaris* should be the name used, since review of cases by Adam and associates[9] suggests that true *Helminthosporium* and *Drechslera* have not caused disease in humans.

Treatment of this mycotic infection is primarily surgical debridement.[3,10,11] Cases have been reported in which a cure was effected by surgical resection without antifungal chemotherapy. Both of our patients required two surgical drainage procedures. Patient 1 received antifungal therapy, whereas Patient 2 was cured with surgery alone. Itraconazole has been reported to have good activity against a single isolate of *Bipolaris*.[13]

The most common finding of sinusitis on computed tomographic scan is the presence of soft-tissue masses of low attenuation in the paranasal sinuses. Our patients had the unusual computed tomographic findings of chronic sinusitis with central areas of high attenuation. This corresponded with the findings of inspissated mucus, with no calcific concretions.

Naul, Hise, and Ruff[14] recently reported similar computed tomographic findings with inspissated mucus in chronic sinusitis. On magnetic resonance imaging studies, these areas of high attenuation were shown on T_1- and T_2-weighted studies to have diminished signal intensity.

Imachi and associates[15] reviewed the routes of optic nerve and chiasmal involvement after sinusitis. With frontal, maxillary, or ethmoidal sinusitus, orbital extension may occur, causing compression or inflammation of the intraorbital optic nerve. Patient 2 had intraorbital invasion resulting in proptosis. Therapy was initiated before optic nerve damage. With ethmoidal or sphenoidal sinusitis, optic nerve changes may occur at the level of the optic canal. This probably occurred in our Patient 1, causing permanent visual loss.

Aspergillus is a well-known cause of orbital involvement after mycotic sinusitis.[16] Our two cases of *Bipolaris* share many similar traits. Both *Aspergillus* and *Bipolaris* usually occur in healthy patients, although orbital involvement with *Aspergillus* has been reported in an immunocompromised patient.[17] Proptosis and optic nerve involvement, as seen in our two cases of *Bipolaris*, have also been reported with *Aspergillus*.[18] The histopathologic findings do differ, however. With *Aspergillus*, dichotomously branching septate hyphae are seen. With *Bipolaris*, distorted fusoidal branching septate hyphae are seen. Therapy in both cases involves surgical debridement.

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Vitrectomy for Impending Idiopathic Macular Holes

William E. Smiddy, M.D., Ronald G. Michels, M.D., Bert M. Glaser, M.D., and Serge de Bustros, M.D.

We performed pars plana vitrectomy in 15 patients with physical changes and visual loss believed to indicate impending macular hole formation. Twelve (80%) of 15 eyes have not progressed to macular holes during a minimum follow-up period of 15 months (average, 26 months). In these 12 patients final vision was within one line of the preoperative vision in four eyes, improved two or more lines in five eyes, and was two lines worse in three eyes. Decreased vision in all three eyes was the result of progressive lenticular nuclear sclerosis. A thin sheet of cortical vitreous fibers was sometimes found intraoperatively on the surface of the retina, despite an apparent complete posterior vitreous detachment.

IDIOPATHIC MACULAR HOLES are believed to occur because of vitreous traction on the fovea, possibly during posterior vitreous separation.[1-10] Gass[11] recently suggested that tangential traction from the posterior vitreous surface is the cause of macular holes and that the initial stage is indicated by loss of the normal foveolar depression and a small, round, yellow spot in the center of the macula.

When an idiopathic macular hole occurs in one eye, the risk of the fellow eye developing a macular hole has been reported to range from 3% to 22%.[6-8,11-18] However, several reports indicate that the risk of macular hole formation is at least 50% if certain characteristics are present. Reported high-risk characteristics include (1) macular cyst and visual acuity of 20/50 or less[8]; (2) cystic retinal or retinal pigment epithelial changes[14]; (3) involutional macular thinning[16]; and (4) slight visual loss, metamorphopsia, and low detachment of the center of the macula.[11]

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Prophylactic therapies to prevent idiopathic macular hole formation based on psychosocial, nutritional, inflammatory, and vascular theories of pathogenesis have been ineffective.[17,18] After formation of a full-thickness macular hole, therapy is not effective other than treating the rare complication of retinal detachment.[4,17,19-21] We report the results and complications of vitrectomy to prevent macular hole formation in a group of 15 eyes we believed to have high-risk characteristics indicative of an impending idiopathic macular hole.

Patients and Methods

Fifteen consecutive patients underwent vitrectomy in an attempt to prevent development of macular holes. Patients were selected for surgery if they had both reduced vision and physical changes in the macula believed to be indicative of impending development of a macular hole. A preoperative history including age, sex, duration and character of symptoms or decreased vision, history of hysterectomy or estrogen treatment, history of systemic hypertension, and history of trauma or other inflammatory events was recorded. The preoperative examination included Snellen visual acuity; refractive error; the type and degree of lens opacity; presence or absence of partial or complete posterior vitreous detachment as assessed by slit-lamp biomicroscopy with a fundus contact lens; and features of the macula including holes, cysts, pigmentary changes, or direct evidence of vitreomacular traction. Fluorescein angiograms were not routinely performed.

During surgery the extent of any posterior vitreous detachment, evidence of vitreomacular traction, anatomic features of the macula, and operative complications were noted. The preexisting vitreoretinal anatomy could often be determined better intraoperatively than preoperatively because of improved visualization

provided by endoillumination and because of dynamic movement of the vitreous gel during vitrectomy.

Postoperatively, progression to a macular hole, other changes in the macular area, visual acuity, status of the lens, and other complications were recorded.

Results

There were 12 women and three men. The average age at the time of surgery was 64 years (range, 44 to 78 years). Two patients were less than 57 years old. Preoperative visual acuity ranged from 20/20 to 20/80, with a mean between 20/40 and 20/50 and a median and mode of 20/50. Fourteen eyes were phakic, including one eye with moderate nuclear sclerosis (Table).

There was an idiopathic macular hole in the fellow eye of 14 patients, with visual acuity ranging from 20/100 to 20/400. The duration of the macular holes was known in 12 of the 14 patients and ranged from one to five years. The macular holes were of two years' duration or less in 11 patients.

Preoperative symptoms were present in all eyes undergoing vitrectomy. The main symptoms were decreased vision in 15 eyes, metamorphopsia in three eyes, and a relative central scotoma in one eye. The duration of symptoms was known in 13 patients, and ranged from one week to 12 months. Symptoms were present for two weeks or less in three patients, two weeks to two months in seven patients, and four to 12 months in three patients. Seven patients had systemic hypertension. Three of the 12 women were taking estrogen, and three had undergone hysterectomy.

In all eyes the preoperative macular appearance was characterized by cystic changes in the deep retina that ranged from small, multiple cystic spaces to a single, large cyst (Fig. 1). Tiny white lines or striae were also sometimes visi-

TABLE

CLINICAL FEATURES OF PATIENTS UNDERGOING VITRECTOMY FOR IMPENDING IDIOPATHIC MACULAR HOLE*

PATIENT NO., AGE (YRS), SEX	VISUAL ACUITY		VITREOUS STATUS†	LENGTH OF FOLLOW-UP (MOS)	LENS STATUS§ (PREOPERATIVE/ POSTOPERATIVE)
	PRE-OPERATIVE	POST-OPERATIVE			
1, 65, F	20/50	20/25	C	41	Clear/clear
2, 65, F	20/50	20/60	C	16	Clear/clear
3, 63, M	20/50	20/50	C	15	Clear/clear
4, 45, F	20/40	20/25	B	24	Clear/clear
5, 58, F	20/20	20/25	A	40	Clear/1+
6, 66, F	20/70	20/30	A	31	2+/Intraocular lens
7, 78, F	20/25	20/200‡	A	47	Clear/2+
8, 71, F	20/30	20/70‡	D	28	Clear/2+
9, 64, F	20/30	20/70‡	A	15	Clear/1+
10, 48, F	20/50	20/25	B	16	Clear/clear
11, 70, F	20/60	20/30	C	22	Clear/1+
12, 69, F	20/30	20/40	C	15	Intraocular lens
13, 66, F	20/70	20/200	B	—¶	Clear/clear
14, 70, F	20/50	20/80	C	—¶	Clear/clear
15, 64, F	20/50	20/70	C	—¶	Clear/clear

*The fellow eye in all patients except Patient 9 had a macular hole. All patients had decreased vision preoperatively except Patient 5 who had a relative central scotoma. Patients 2, 3, and 8 also had metamorphopsia.

†Vitreous status judged intraoperatively: A, no posterior vitreous detachment; B, posterior vitreous detachment with cortical vitreous fibers present on the inner surface of the macula; C, posterior vitreous detachment without cortical vitreous fibers; and D, partial posterior vitreous detachment.

‡Final postoperative visual acuity in patients with progressive lenticular nuclear sclerosis. Best postoperative visual acuity was within one line of preoperative visual acuity in two patients before the cataract developed, and in the third patient, the Potential Acuity Meter reading was one line better than preoperative visual acuity.

§1+, mild nuclear sclerosis; 2+, moderate nuclear sclerosis.

¶Follow-up irrelevant because of development of full-thickness macular hole.

detachment, but with pigment epithelial defects, 86% progressed to a full-thickness macular hole.

The status of the vitreous gel is a critical component of the vitreous traction theory of idiopathic macular hole formation. However, there is considerable difficulty in visualizing the posterior vitreous surface clinically. A precorneal lens or a corneal contact lens is necessary to visualize the posterior part of the vitreous cavity, but visualization of the vitreous gel is often difficult, especially if there is substantial liquefaction. Signs of a posterior vitreous detachment may sometimes be seen by indirect ophthalmoscopy, especially if a Weiss' ring is present representing glial remnants of a previous vitreopapillary attachment. Still, in some eyes the status of the posterior vitreous surface cannot be accurately determined clinically. Vitreous dynamics as seen with endoillumination during vitrectomy are probably the most accurate means of determining the actual status of the posterior vitreous surface.

Partial posterior vitreous detachment has been described clinically[2,9,10,28,29] and histopathologically[24,25] in eyes with idiopathic macular holes. This was noted preoperatively in one of our patients. In three other eyes a separate, thin, cortical vitreous layer was demonstrable on the retina intraoperatively, despite apparent coexistent posterior vitreous detachment.

Surgical objectives of vitrectomy for impending idiopathic macular hole center on lysing any posterior vitreomacular adhesions. This is easiest if there is a partial posterior vitreous detachment with a zone of vitreomacular adhesion. If no posterior vitreous detachment is present, the posterior cortical vitreous is engaged by using suction or a vitreoretinal pick and peeled from the inner retina. The cortical vitreous usually separates readily from the retina. If an apparent posterior vitreous detachment is present, a vitreoretinal pick or tapered-tip suction needle is used to search along the inner retinal surface surrounding the macula (Fig. 2). Fine strands can sometimes be identified adjacent to the macula, as found in three of our cases. These fibers indicate that a thin layer of cortical vitreous remains that can usually be elevated and removed (Fig. 3).

No direct macular damage was evident during surgery in any case, including the three eyes that progressed to a full-thickness defect. Whether the progression was inevitable and incidental to the surgery or hastened by the operative procedure is not apparent.

No serious posterior segment complications occurred in this series other than progression to a macular hole in three eyes. One possible peripheral retinal tear was treated with cryotherapy. Progressive cataract formation occurred in five (36%) of the 14 phakic patients. This is consistent with the observation of postoperative nuclear sclerosis in 34% to 39% of

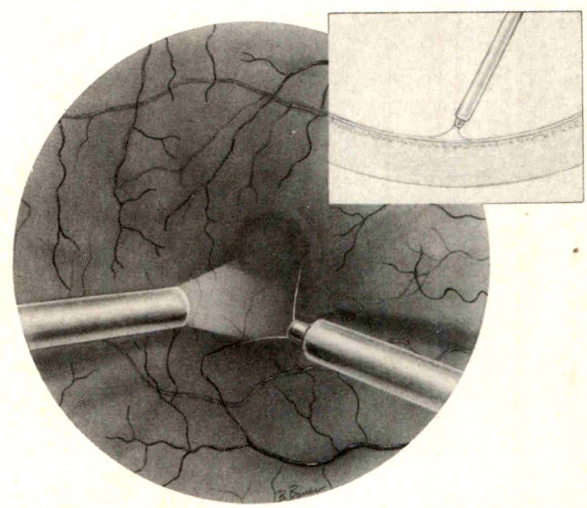


Fig. 2 (Smiddy and associates). Tapered-tip suction needle used to identify and separate thin cortical vitreous sheet on inner retinal surface. Vitreous is first identified as subtle strands as traction is applied to cortical vitreous layer.

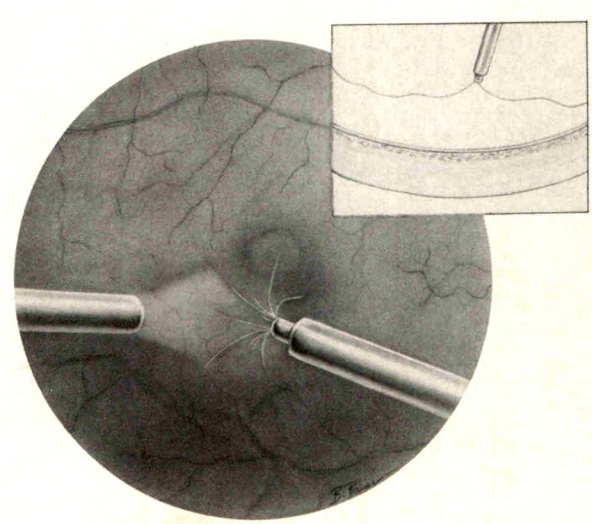


Fig. 3 (Smiddy and associates). Cortical vitreous sheet is separated from retina by applying anteroposterior suction force with tapered-tip needle and engaging the vitreous in different locations surrounding the macula. After the vitreous sheet is completely separated from the retina, it is excised with the vitrectomy probe (not shown).

patients after vitrectomy for macular pucker.[30-32] The cause of nuclear sclerosis is unknown.

This study lacks a concurrent control population, and the eyes operated on may not be entirely comparable to those in studies that have identified characteristics correlating with a high risk of idiopathic macular hole formation. Also, the length of follow-up in our series is shorter than in some natural progression studies. However, the relatively low rate of subsequent idiopathic macular hole formation in our high-risk patients (three of 15) compares favorably with other studies of high-risk patients reporting at least a 50% incidence of subsequent idiopathic macular hole formation. We believe that the role of vitrectomy as a treatment for impending idiopathic macular hole formation should be evaluated further, possibly in the context of a randomized clinical trial.

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Peripheral Retinal Cryopexy for Subtotal Vitreous Hemorrhage

William H. Ross, M.D., and Michael J. Gottner, M.D.

We used peripheral retinal cryopexy to treat 20 eyes in 15 patients with subtotal vitreous hemorrhage secondary to proliferative diabetic retinopathy. In 18 eyes, complete panretinal photocoagulation had been performed before the subtotal vitreous hemorrhage and the subsequent cryopexy. The length of follow-up averaged 16 months. The vitreous hemorrhage completely cleared in 11 eyes (55%) and partially cleared in six eyes (30%). Visual acuity after treatment improved in 13 eyes (65%), remained unchanged in six eyes (30%), and decreased in one eye (5%).

DIABETIC RETINOPATHY is the leading cause of blindness in North Americans between the ages of 30 and 60 years. Better diabetic control, the use of multiple daily injections of insulin and infusion pumps, and improved education will increase the life expectancy of diabetic patients. Therefore, the complications of diabetes, including vitreous hemorrhage and tractional retinal detachment, are likely to increase. While panretinal photocoagulation has been shown to be effective in reducing the risk of vitreous hemorrhage and tractional retinal detachment in patients with proliferative diabetic retinopathy,[3,4] vitreous hemorrhage still occurs. Early vitrectomy for vitreous hemorrhage has been advocated by some researchers,[5,6] but the complications and morbidity of vitreous surgery are significant.[7,8] Because of the risks of early vitrectomy, there has been renewed interest in the use of peripheral retinal cryopexy in the treatment of patients with vitreous hemorrhage secondary to proliferative diabetic retinopathy.[9-12] We studied 20 eyes in 15 patients with subtotal vitreous hemorrhage secondary to proliferative diabetic retinopathy treated with peripheral retinal cryopexy and evaluated the effect on visual acuity, clearing of vitreous hemorrhage, and recurrent vitreous hemorrhages.

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Patients and Methods

Twenty eyes in 15 patients with proliferative diabetic retinopathy who developed one or more recurrent subtotal vitreous hemorrhages from disk or retinal neovascularization, despite panretinal photocoagulation, were included in this study. Eighteen of the eyes had previously undergone panretinal photocoagulation using between 1,500 and 3,000 burns of 200- to 500-μm spot size.

We allowed three months for the vitreous hemorrhage to clear before determining that further laser photocoagulation was not possible because of hazy media. Subtotal vitreous hemorrhage was defined as bright red blood within the vitreous cavity, which obscured the posterior pole. In most cases, the hemorrhage was darker red and more dense inferiorly. In all cases, at least 50% of the far peripheral retina superiorly was visible with the indirect ophthalmoscope.

Ultrasonic examination was performed preoperatively in all eyes to rule out the presence of traction retinal detachments. Patients with dense yellow ocher or total red vitreous hemorrhage with no view of the peripheral retina and patients with ultrasonic evidence of traction detachment of the posterior pole were not included in the study and were treated with vitrectomy surgery.

All treatments were performed in the opera-

ting room by using either retrobulbar blocks with intravenous sedation or general anesthesia. The pupil was dilated with one drop each of phenylephrine 2.5% or 10% and cyclopentolate 1% every ten minutes for 30 minutes preoperatively. The technique was similar to that described by Mosier, Del Piero, and Gheewala.[12] A 360-degree conjunctival peritomy was performed. The recti muscles were isolated and a 4-0 black silk suture was placed beneath each muscle to improve manipulation during surgery. Using a 2.5-mm retinal cryoprobe, the superior retina was treated under direct visualization using the indirect ophthalmoscope. A tip temperature of −60 C was achieved. The end point of each treatment was a soft white retinal opacity, which was usually evident after five to ten seconds. Applications beneath the recti muscles, because of the thinner sclera in this location, were usually of two to three seconds' duration. Three rows of four to five evenly spaced applications were made in each of the four quadrants. The anterior applications were made at the level of an imaginary line connecting the insertions of the recti muscles. This approximates the location of the ora serrata. The posterior applications were made at the equatorial region. Each treatment spot was placed approximately one spot size apart. No treatments were made posterior to the equator for fear of increasing contraction of possible preexisting epiretinal membranes.[9] When visualization was not possible because of dense vitreous hemorrhage, especially in the inferior quadrants, the average time needed to produce a soft white lesion in the upper quadrants was used. A total of 48 to 60 applications were made between the ora serrata and the equator in each eye treated.

After treatment, the muscle sutures were removed and the conjunctiva reapproximated using interrupted 6-0 plain sutures. Gentamicin ointment was applied and the eye was patched. Total operating time was approximately 40 minutes. Most of the patients were discharged from the hospital on the first postoperative day. Patients were monitored for clearing of vitreous hemorrhage, improvement of visual acuity, the development of recurrent vitreous hemorrhage, and surgical complications.

Twenty eyes in 15 patients were treated (Table). Eight patients were women and seven were men. They ranged in age from 34 to 76 years (average, 65 years). The duration of diabetes mellitus ranged from ten to 41 years (average, 21 years). Twelve right eyes and eight left eyes were treated. All eyes were phakic. Extensive panretinal photocoagulation had been performed in 18 of the 20 eyes before the vitreous hemorrhage and the retinal cryopexy. Vitreous hemorrhage on initial examination prevented complete panretinal photocoagulation in two patients (Patients 6 and 13), where only 50% and 10%, respectively, of the peripheral retina could be treated.

Results

The postoperative follow-up period ranged from 12 to 21 months (average, 16 months). After treatment, there was clearing of the vitreous hemorrhage in 17 of the 20 eyes. The vitreous hemorrhage cleared completely in 11 eyes and partially in six eyes. In three eyes, the vitreous hemorrhage did not clear (Fig. 1). Two eyes with nonclearing hemorrhages have recently undergone vitrectomy surgery. Patient 7, who is in renal failure and on peritoneal dialysis, suffered a stroke and no further treatment was performed on his left eye.

Of the 11 eyes that showed complete reabsorption of the vitreous hemorrhage, seven cleared completely within eight weeks. In the remaining four eyes, the hemorrhage had cleared by 13 weeks. After 13 weeks, ten of these 11 eyes remained free of any further hemorrhage. Patient 7 suffered a rebleed in his right eye five months after treatment. This rehemorrhage slowly cleared over a two-month period and he has not suffered any further hemorrhage.

After reabsorption of the vitreous hemorrhage, it was possible to visualize atrophic vessels on the optic disk or along the major retinal vessels in eight of 11 eyes. These atrophic vessels were presumably the source of the previous vitreous hemorrhage. In three eyes, there was persistent disk and retinal neovascularization and further panretinal laser photocoagulation therapy was applied. This retreatment produced complete regression of the disk and retinal vessels in two eyes and partial regression in the third.

Recurrent vitreous hemorrhage occurred in five eyes (25%) (Fig. 1). One case of tractional

TABLE
SUMMARY OF CLINICAL DATA

PATIENT NO., AGE (YRS), SEX	NO. OF YEARS DIABETIC	TREATED EYE	ANES-THETIC	% OF PREOPERATIVE PANRETINAL PHOTOCOAGULATION	VISUAL ACUITY*		LENGTH OF FOLLOW-UP (MOS)	VITREOUS CLEARING	REGRESSION OF RUBEOSIS IRIDIS †	RECURRENT VITREOUS HEMORRHAGE
					PREOPERATIVE	POSTOPERATIVE				
1, 66, F	41	R.E.	General	100	HM	20/80	21	Complete	N/A	No
		L.E.	General	100	HM	20/80−2	16	Complete	N/A	No
2, 72, F	23	R.E.	Local	100	HM	HM	19	Partial	Complete	Yes
		L.E.	Local	100	HM	CF	13	Complete	N/A	No
3, 61, M	21	R.E.	General	100	20/200	20/50+1	19	Complete	N/A	No
4, 61, M	20	R.E.	General	100	HM	20/200	19	Complete	Complete	No
5, 76, M	26	R.E.	General	100	CF	20/50	16	Complete	N/A	No
6, 74, F	19	L.E.	Local	50	HM	HM	16	None	N/A	No
7, 48, M	19	R.E.	General	100	HM	CF	16	Complete	N/A	Yes
		L.E.	General	100	HM	HM	16	None	N/A	Yes
8, 67, M	15	L.E.	Local	100	HM	20/400	13	Complete	N/A	No
9, 72, M	24	L.E.	General	100	CF	20/200	19	Partial	N/A	Yes
10, 56, F	26	R.E.	Local	100	20/400	20/80	18	Complete	N/A	No
11, 34, F	24	R.E.	General	100	20/50	20/200	16	Partial	N/A	No
		L.E.	General	100	CF	20/200	16	Partial	N/A	Yes
12, 76, F	10	R.E.	Local	100	20/200	20/80	19	Complete	N/A	No
13, 77, F	12	R.E.	General	10	CF	CF	13	Partial	N/A	No
14, 67, F	22	R.E.	General	100	20/200	20/200	12	Partial	N/A	No
		L.E.	General	100	20/400	20/80	12	Complete	N/A	No
15, 61, M	15	R.E.	General	100	HM	HM	12	None	Complete	No

*HM, hand motions; CF, counting fingers.

†N/A, not applicable, rubeosis iridis not present before treatment.

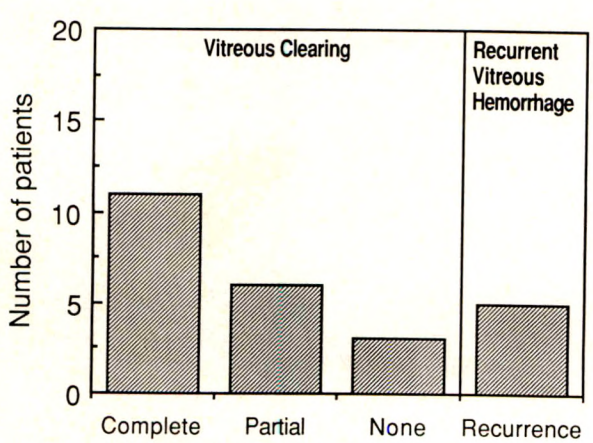


Fig. 1 (Ross and Gottner). Vitreous hemorrhage completely cleared in 11 of 20 eyes (55%), partially cleared in six eyes (30%), and did not clear in three eyes (15%). Vitreous hemorrhage recurred in five eyes (25%).

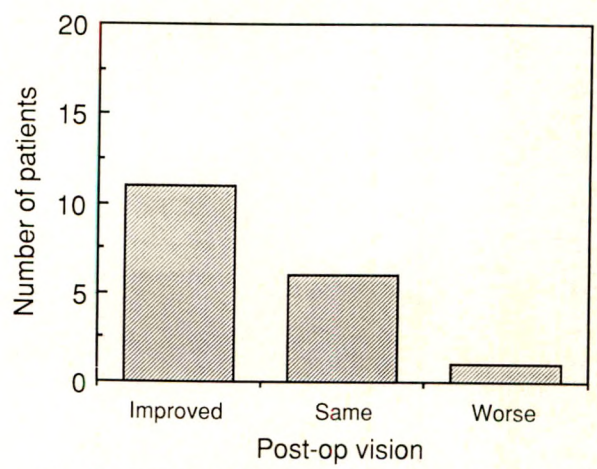


Fig. 2 (Ross and Gottner). Postoperatively, visual acuity improved in 13 of 20 eyes (65%), remained unchanged in six eyes (30%), and worsened in one eye (5%).

retinal detachment developed postoperatively. Visual acuity improved in 13 eyes, remained unchanged in six eyes, and decreased in one eye (Fig. 2). In three eyes with rubeosis iridis as well as vitreous hemorrhage, complete regression of the iris neovascularization was noted after treatment. In two of these eyes, the rubeosis iridis involved only the pupillary margin preoperatively. In the third case (Patient 15), there was evidence of extensive rubeosis with closure of the anterior chamber angle from the 8 o'clock to the 4 o'clock meridian. Only the inferior angle remained open. After peripheral retinal cryopexy, the iris vessels regressed and the inferior angle continued to be patent. Intraocular pressure in this patient has been controlled with one drop of timolol maleate 0.5% twice daily. In three of the 20 eyes treated with peripheral retinal cryopexy, the eye treated was the one eye with useful vision. In two of these patients, the other eye had undergone unsuccessful vitrectomy surgery for vitreous hemorrhage and traction detachments (Patients 5 and 9). The third patient (Patient 10) showed evidence of massive proliferative vitreoretinopathy in her left eye, which was believed to be inoperable.

Discussion

The Diabetic Retinopathy Study demonstrated that panretinal photocoagulation can produce regression of disk and retinal neovascularization and prevent severe visual loss in patients with diabetic retinopathy who have high-risk characteristics.[3,4] Panretinal photocoagulation presumably decreases the production of a vasoproliferative factor by the ischemic retina and induces regression of the disk and retinal neovascularization. The same mechanism is believed to account for the regression of iris neovascularization. However, despite panretinal photocoagulation, 20.1% of patients with high-risk characteristics suffer recurrent vitreous hemorrhage.[4] Once vitreous hemorrhage occurs, further laser therapy is not possible, and other treatment modalities must be considered.

Early vitrectomy in these patients has been advocated by Shea, Young, and Howcroft[5] and Blankenship and Machemer.[6] However, complications of vitrectomy are considerable[7,8] and include rubeosis iridis in 13% of phakic eyes and 32% of aphakic eyes, iatrogenic retinal breaks during surgery in 20% of cases, postoperative retinal detachments in 16% of cases, intraoperative and postoperative vitreous hemorrhage in 4% and 29% of cases, respectively, and visually significant lens opacities in 17% of phakic eyes. Reoperation in up to 25% of eyes with vitrectomies has been reported secondary to retinal detachment or nonclearing of vitreous hemorrhage.[7,8] Many patients with proliferative diabetic retinopathy are also medically unstable and some are undergoing peritoneal or hemodialysis. Therefore, there can be a significant degree of morbidity in these patients undergoing prolonged surgical procedures.

Peripheral cryopexy offers a less invasive form of management in diabetic patients with subtotal vitreous hemorrhage and has, therefore, been advocated.[9-13] As with panretinal photocoagulation, the supposed mechanism of action is to decrease the production of a vasoproliferative factor, the stimulus for neovascularization, by ablating the peripheral ischemic retina. The result is regression of existing disk and retinal neovascularization and the prevention of further vitreous hemorrhage. Histologic studies of thermal lesions resulting from diathermy, photocoagulation, and cryopexy have been studied extensively[14,15] and have been found to produce similar retinal destruction.

Clinically, we were impressed with the rapid reabsorption of the vitreous hemorrhage after peripheral retinal cryopexy. On the first postoperative day, it is often possible to obtain a gross view of the posterior pole. In seven of 11 eyes that cleared completely, the hemorrhage was totally reabsorbed by eight weeks. By 13 weeks, the remaining four eyes had cleared. The relatively rapid clearing of the vitreous hemorrhage differs significantly from the slow absorption of vitreous blood that occurs in untreated eyes. Although the exact mechanism of this rapid clearing is not known, the choroidal lesions produced by cryopexy may aid the reabsorption of hemorrhage by producing inflammatory changes in the blood-retinal barrier. Alterations of the retinal pigment epithelium may also be a factor in this rapid clearing.

In this study, complete clearing of vitreous hemorrhage was achieved in 11 eyes (55%) and partial clearing was achieved in six eyes (30%); three eyes (15%) did not clear (Fig. 1). Visual acuity improved in 13 eyes (65%) (Fig. 2). Visual acuity of 20/200 or better was achieved in 11 eyes (55%). In three patients, the treated eye

was the only eye with useful vision and these patients regained independence and were able to move about freely and care for themselves without the risk of vitrectomy.

Our results are similar to those reported by Mosier, Del Piero, and Gheewala.[12] They found complete vitreous clearing in 56% of their cases, improvement in visual acuity in 65%, and a visual acuity of 20/200 or better in 56%. In a series of 100 cases reported by Daily and Gieser,[11] complete clearing of the vitreous hemorrhage was achieved in 75% of patients and improved vision in 46%. In their series, 83% of patients achieved a visual acuity of 20/200 or better.

Tractional retinal detachment with macular involvement occurred in one of our patients. This 5% incidence is similar to that reported previously. Mosier, Del Piero, and Gheewala[12] reported a 4% incidence (one of 24 eyes), Benedett and associates[13] found a 3.2% incidence (five of 158 eyes), and Daily and Gieser[11] found a 6% incidence (six of 100 eyes) of traction detachments. These figures are much lower than those reported by Oosterhuis and Bijlmer-Gorter[9] and Ramsay, Cantrill, and Knobloch.[10] In Oosterhuis and Bijlmer-Gorter's[9] series of 21 cases, seven (33%) were found to have traction detachments after clearing of the vitreous hemorrhage. However, preoperative ultrasound studies were not performed to determine if the traction detachments were present before cryopexy. In Ramsay, Cantrill, and Knobloch's[10] series of 14 cases, five (36%) developed traction detachments after cryoablation. In both of these series, the cryoapplications were made posterior to the equator, and, in many cases, confluent applications were made to the level of the vascular arcades. Their high incidence of traction detachments may have been caused by these posterior applications of cryopexy with resultant inflammation of the vitreous and secondary contraction of preexisting fibrovascular membranes. Lincoff and McLean[16] described vitreoretinal adhesions and condensation of vitreous fibrils at the point of excessive cryoapplication. They postulated that the fibrils may also have been indirectly damaged by cryopexy-induced uveitis.

Recurrent vitreous hemorrhage occurred in five eyes, or 25% of our cases.[2] These results are similar to those reported by Mosier, Del Piero, and Gheewala[12] and Benedett and associates.[13]

Regression of rubeosis iridis was noted in three treated patients. A similar result was reported by Ramsay, Cantrill, and Knobloch[10] in three patients with rubeosis. Again, this is believed to be secondary to the decreased production of angiogenesis factor by the ischemic retina.

In view of the good result in this study and in that reported by Mosier, Del Piero, and Gheewala[12] using peripheral cryotherapy as well as the low incidence of complications, the following protocol in the management of patients with proliferative diabetic retinopathy seems reasonable. All patients with proliferative diabetic retinopathy and high-risk characteristics[4] should undergo panretinal photocoagulation therapy in an attempt to induce regression of the disk and retinal neovascularization. If vitreous hemorrhage occurs despite panretinal photocoagulation and if the hemorrhage is subtotal, peripheral cryopexy treatment should be performed as described. In one case in this series and in another reported by Mosier, Del Piero, and Gheewala[12] a patient with a visual acuity of 20/50 or better developed a tractional retinal detachment with macular involvement and resultant severe loss of visual acuity. Therefore, in patients with a visual acuity of better than 20/200, observation for spontaneous clearing of vitreous hemorrhage is advisable so that additional panretinal photocoagulation can be performed. Patients with unresolved total vitreous hemorrhage and tractional detachments with macular involvement should undergo vitrectomy.

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OPHTHALMIC MINIATURE

His right eye gradually regained normal vision, and his left eye, though oddly 'stained,' regained enough sight to help its colleague. He had worn glasses before, and now with perceptibly thicker lenses was able to envisage, and then attain, a return to an ordinary life of walking and reading. The situation was even likely to improve further, and he might expect to be able to drive a car again. 'You don't just see with your eyes, you see with your brain,' his cheerful doctor told him, 'and it's amazing what ingenious adjustments it can make!' The same doctor assured him that his 'funny eye,' certainly noticeable, looked 'fascinating,' even 'positively attractive.'

Iris Murdoch, *The Book and the Brotherhood*
New York, Viking Penguin Inc., 1988, p. 93

Immunohistopathologic Findings in Proliferative Diabetic Retinopathy

Christophe Baudouin, M.D., Danielle Fredj-Reygrobellet, Ph.D., Philippe Lapalus, Ph.D., and Pierre Gastaud, Ph.D.

We performed immunopathologic studies on pars plana specimens obtained by biopsy in patients with diabetes mellitus type I or II and by autopsy in diabetic patients and normal subjects. Frozen sections were treated with several antisera, including anti-IgG, complement components, and major histocompatibility complex antigens, as well as anti-factor VIII to detect vascular structures. The results showed IgG in a linear pattern at the basal pole of pigment epithelial cells and complement deposits of C3c, C3d, and C4 at the same location and in the stroma. HLA-DR expression was found at the level of the pigmented cells. These data suggest that some autoimmune processes may be involved in proliferative diabetic retinopathy at the level of the pigment epithelium, but it is unknown whether they are an epiphenomenon of neovascularization or if they play a role in its initiation.

THE EXTERNAL BLOOD-RETINAL barrier is essentially localized at the level of the retinal pigment epithelium and plays a major role in diffusion phenomena (particularly in exchanges between blood and retinal extravascular spaces). Thus, the retinal pigment epithelium is involved in blood-retinal barrier disruptions in ocular vascular diseases, such as diabetic retinopathy, where its damages are evident from the earliest stages, as shown in color vision studies[1,2] or vitreous fluorophotometry.[3]

The pathogenesis of proliferative diabetic retinopathy is poorly understood. Rahi and Addison[4] suggested that immunogenic mechanisms may play a role in the development of microangiopathy.[4] Few histopathologic studies of proliferative retinopathy in humans have been conducted, and we undertook this study to determine the immunopathologic changes at the level of the retinal pigment epithelium in diabetic patients. We also focused on the detection of class II antigens (HLA-DR), since they have been implicated in autoimmune diseases.

Material and Methods

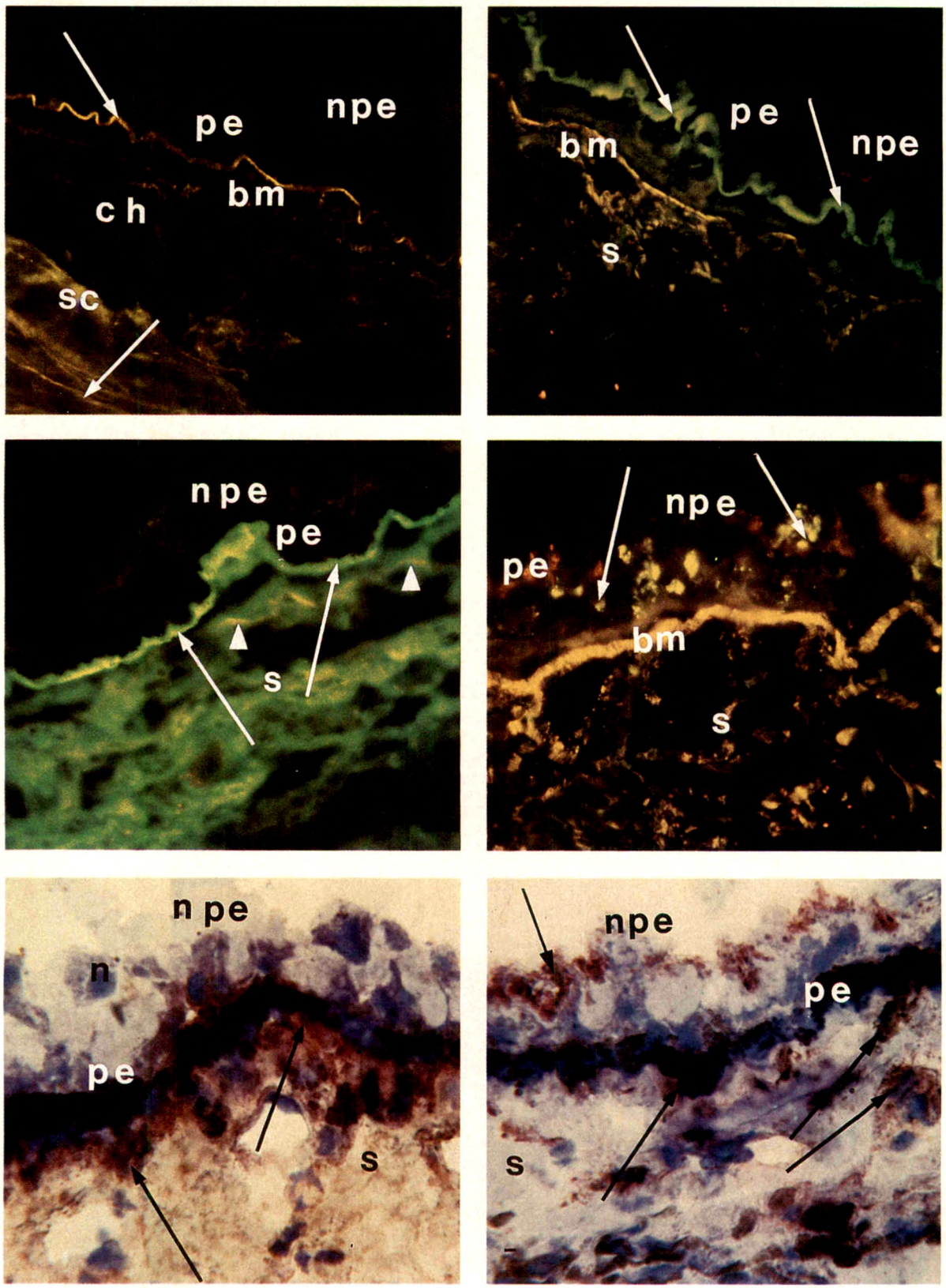
We obtained biopsy specimens from 16 patients aged 36 to 86 years. Eight specimens were taken from eight normal subjects at autopsy performed within ten hours after death. None of these subjects were known to have autoimmune or ocular disease and the eyes were normal, as assessed by slit-lamp examination. Eight biopsy specimens were taken from patients with insulin-dependent diabetes (five patients had type I and three had type II) and severe proliferative retinopathy. One of these specimens was taken at autopsy and the others were obtained by biopsy of the pars plana during vitrectomy for intravitreal hemorrhages. These specimens included a piece of eye wall with pigment and nonpigment epithelia, and underlying choroid. The specimens taken at autopsy included sclera. The specimens, each 1.5 to 2 mm in size, were immediately embedded in OCT compound, frozen in liquid nitrogen, and stored at −80 C.

Antibodies—We used 19 monoclonal or polyclonal antibodies in this study. Fluorescein isothiocyanate-conjugated rabbit anti-human IgG, IgM, IgA, IgD, and IgE antisera; antifibrinogen; and four antisera directed against complement components (C1q, C3c, C3d, and C4) were purchased from Dakopatts, Copenhagen, Denmark. IgG were also identified with mouse anti-human Fc IgG monoclonal

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antibody (Immunotech, Marseille, France). Rhodamine isothiocyanate-labeled anti-factor VIII antiserum (Dakopatts) was used to identify endothelial cells in blood vessels. The mouse monoclonal antibody (W6/32) directed against the common determinant of human HLA-A, -B, and -C (Sera-Lab, Crawley Down, Sussex, England) and three monoclonal antibodies directed against the nonpolymorphic region of the HLA-DR, anti-human DR1 (Bethesda Research Laboratories, Gaithersburg, Maryland), I2 (Coulter, Hialeah, Florida), and G157 anti-HLA-DR (Dr. Bernard, Gustave Roussy Institute, Paris, France) were used. Additional monoclonal antibodies were used to identify T lymphocytes (OKT3, Ortho Diagnostic Systems, Raritan, New Jersey), B lymphocytes (B4, Coulter), and monocytes (MO2, Coulter). All monoclonal antibodies were detected with a fluorescein isothiocyanate-labeled rabbit anti-mouse immunoglobulin antiserum (Dakopatts). These reagents were all used in a 1:50 dilution in phosphate buffered saline (pH, 7.4), except anti-IgG and C3d, which were used in a 1:100 dilution.

Immunofluorescence—Cryostat frozen sections 5 μm thick were prepared and air dried at room temperature. No fixation was used. Sections were first incubated for 30 minutes with rhodamine-conjugated anti-factor VIII antiserum. After washing in phosphate-buffered saline, sections were reacted with each specific antibody, according to direct or indirect immunofluorescence procedures. Antibodies directed against immunoglobulins, complement components, and fibrinogen were applied for 30 minutes before washing three times in phosphate-buffered saline. The other antibodies were incubated for 90 minutes and then demonstrated by fluorescein isothiocyanate-conjugated rabbit anti-mouse immunoglobulin antiserum. Some of the sections were counterstained with propidium iodide.[5] After the last incubation, the sections were washed in phosphate-buffered saline for five minutes, and then mounted. Fluorescein isothiocyanate and propidium studies were performed under epi-illumination.

Immunoperoxidase procedure—Immunochemistry was performed for HLA-DR antigens and IgG detection by the avidin-biotin peroxidase complex method. Frozen sections were fixed in acetone for ten minutes. After incubation at room temperature for one hour with monoclonal antibody (DR1, I2, G157, HLA-DR, and anti-human Fc IgG), the slides were washed in Tris buffered saline and the secondary antibody (Dakopatts), biotin-conjugated horse anti-mouse IgG (1:400), was layered on the sections for 30 minutes. After washing in Tris buffered saline, avidin-biotin peroxidase complexes (Dakopatts) at a 1:100 dilution were applied for 30 minutes. The slides were rewashed and developed in aminoethyl carbazole hydrogen peroxide solution. They were then counterstained with Harris hematoxylin, dehydrated, and mounted in mounting medium before examination.

Results

Normal tissues—Examination of normal pars plana sections showed only a few IgG (Figure, top left), IgM, IgA, and fibrinogen deposits in the stroma and in the rare blood vessels detected by anti-factor VIII. IgD and IgE were negative and no complement deposits could be seen. The reactivity of W6/32 was weak and

Figure (Baudouin and associates). Top left, Pars plana from a normal subject incubated with anti-IgG. Only Bruch's membrane and some elastic fibers in the sclera are autofluorescent (arrows). The same patterns were found with all of the tested antibodies, except with anti-HLA-DR, which sometimes stained some scattered cells in the stroma. pe, pigment epithelium; npe, nonpigment epithelium; bm, Bruch's membrane; sc, sclera; ch, choroid (×100). Top right, Pars plana from a patient with proliferative diabetic retinopathy, incubated with anti-IgG. Note the linear deposits underlining the pigmented cells (arrows). s, stroma (×150). Middle left, Pars plana incubated with anti-C3c shows almost the same patterns as specimens incubated with anti-IgG (arrows). Stroma also shows C3c deposits. Bruch's membrane (arrowheads) is partially masked by the stromal deposits of C3c (×150). Middle right, Localization of class II antigens (arrows) in the retinal pigment epithelium (HLA-DR1, I2, and G157 monoclonal antibodies) (×150). Bottom left, Immunoperoxidase staining of IgG deposits (arrows) under the pigment epithelial cells of the pars plana (Harris hematoxylin counterstains the nuclei). The dark-stained material is the melanine pigment, and the product localizing the antibodies is red brown. n, nucleus (×200). Bottom right, Expression of class II antigens (arrows) as identified by immunoperoxidase staining on pigment and nonpigment epithelial cells. Some stromal cells show positive reaction (×200).

irregularly noted on pigment epithelial cells. The expression of class II antigens was limited to rare single cells scattered throughout the stroma and endothelial cells of the blood vessels did not show a detectable staining with anti-HLA-DR. The three monoclonal antibodies directed against HLA-DR (HLA-DR1, I2, and G157) disclosed the same distribution and patterns. No lymphocytes or monocytes could be detected. None of the antibodies reacted with the retinal pigment epithelium.

Tissues from patients with proliferative retinopathy—Examination of normal as well as pathologic pars plana specimens did not show any histologic anomaly by hematoxylin and eosin staining. The results of immunofluorescence reactivity are given in the Table. Moderate amounts of IgG, IgM, IgA, and fibrinogen were observed in the stroma, but the basal pole of the pigment epithelial cells was underlined with abundant, linear deposits of IgG (Figure, top right), IgA, and fibrinogen, as well as C3c (Figure, middle left) and C3d. Whether or not these antibodies are localized within the basal cytoplasm, the basal lamina, or both, remains to be determined by electron microscopic studies, which are currently in progress. Diffuse stromal positivity was constantly observed with C3c and C3d, sometimes masking Bruch's membrane (Figure, middle left). C4 was positive in the stroma in five of eight specimens. IgD, IgE, and C1q were negative in all specimens. The reactivity of all these antisera was not correlated with the type of diabetes, and type I or type II diabetic patients showed the same reactivity patterns. Moreover, the sample obtained by autopsy showed the same results as biopsy specimens.

HLA-DR antigens, detected by HLA-DR1, I2, and G157 monoclonal antibodies, were expressed in a similar way on pigment and nonpigment epithelial cells in six of eight specimens (Figure, middle right). The three monoclonal anti-HLA-DR antibodies gave the same results. Not all of the epithelial cells stained uniformly and this often resulted in heterogeneous or patchy staining. The same number of HLA-DR-positive cells were present in the stroma of specimens from patients with proliferative retinopathy as from normal controls, and T3, B4, and MO2 antibodies were negative.

Immunoperoxidase analysis disclosed findings similar to those obtained with immunofluorescent staining (Figure, bottom left and right) and confirmed HLA-DR expression on pigment and nonpigment epithelial cells, both on the membrane and within the cytoplasm.

TABLE

IMMUNOFLUORESCENCE REACTIVITY OF PARS PLANA SPECIMENS FROM EIGHT INSULIN-DEPENDENT DIABETIC PATIENTS WITH PROLIFERATIVE RETINOPATHY*

ANTIGENS	STROMA	BLOOD VESSELS	BRUCH'S MEMBRANE	PIGMENT EPITHELIUM	NON-PIGMENT EPITHELIUM
IgG	±	+	−	+	−
IgM	±	+	−	−	−
IgA	±	+	−	+	−
IgD	−	−	−	−	−
IgE	−	−	−	−	−
C1q	−	−	−	−	−
C3c	+	+	+	+	−
C3d	+	+	+	+	−
C4	+	+	−	−	−
Fibrinogen	+	+	−	+	−
HLA-DR	+	+	−	+	+
HLA-ABC	+	+	−	+	+
T lymphocytes	−	−	−	−	−
B lymphocytes	−	−	−	−	−
Monocytes	−	−	−	−	−

*+, strongly reactive; ±, weakly reactive; −, no reaction.

Discussion

Autoimmune phenomena have already been presumed in diabetic retinopathy[4] and in diabetic nephropathy, where IgG, IgM, and complement deposits have been found in the glomerular basement membrane.[6,7] The findings in these studies together with our findings showing large amounts of IgG, IgA, and complement components in the stroma and underlining the pigment epithelium support the involvement of mechanisms in proliferative retinopathy other than metabolic vascular damage. The absence of abnormal perivascular accumulation of immunoglobulins and complement contrasting with the brightly green reactive pigment epithelium does not suggest simple passive extravascular diffusion, and their linear pattern does not suggest immune complex deposits.

Moreover, HLA-DR expression on pigment and even nonpigment epithelial cells raises the question of possible autoimmune phenomena.

Class II antigens are involved in antigenic presentation to immunocompetent cells. In the normal state, these antigens are restricted to B and activated T lymphocytes, to antigen-presenting cells, and to vascular endothelial cells but are not found on most epithelial cells. Their deviant expression has been pinpointed on thyrocytes in Graves' disease,[8] on beta cells of Langerhans islets in insulin-dependent diabetes,[9] and in graft rejection or graft vs host disease.[10] Studies of their distribution in normal uvea[11,12] localized only a few HLA-DR-positive cells scattered throughout the stroma, whereas epithelial cells were always negative. In retinitis pigmentosa, Detrick and associates[13] observed aberrant HLA-DR expression on pigment epithelial cells.

The presence of these antigens is still not clearly understood, but it has been suggested that it could be the result of lymphocyte interactions.[14,15] However, a study on the pancreas in type 1 diabetic patients[9] demonstrated HLA-DR expression on beta cells of islets without insulitis. Likewise, we did not find any inflammatory cells in our eight specimens from patients with diabetic retinopathy. Gamma interferon has also been supposed to play a major role in HLA-DR expression. This lymphokine has been shown to induce class II antigen expression on many different cells in culture, such as thyrocytes,[16] astrocytes,[17] keratinocytes,[18] and corneal endothelial and stromal cells.[19,20] Detrick and associates[21] detected HLA-DR expression on retinal pigment epithelial cell cultures after adding a solution containing 500 units/ml of gamma interferon. We also found that these cells can be induced to express class II antigens with a single dose of gamma interferon as low as 1 unit/ml (unpublished data). However, even if mechanisms triggering abnormal HLA-DR expression are not well known, it has been proposed[22] that persistent induction of DR antigens at sites where they do not normally exist would result in autoimmunity by converting the target cell into a functional antigen-presenting cell.

Our findings of IgG, IgA, and complement deposits together with class II antigen expression indicate some autoimmune phenomenon at the pigment epithelium level, but we do not know whether this possible autoimmune reaction is directed against the cells themselves or against phagocytized vitreoretinal antigens present at their basal pole. Moreover, it is currently impossible to determine if these autoimmune processes are an epiphenomenon of neovascularization or if they play a role in its initiation. Nevertheless, our data suggest an autoimmune disturbance in patients with proliferative diabetic retinopathy and should lead to further study for a better understanding of this disease process.

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OPHTHALMIC MINIATURE

But even as he lay there, even it seemed later as he was falling, he knew that whatever else might have been damaged, something frightful had happened to his eyes. The pain was extreme, but worse than the pain was the sense that both were injured, and one of the precious orbs actually crushed. He got up slowly, wondering if he had also broken a limb. The centre of his field of vision seemed to have disappeared and the periphery was full of grey bubbling atoms. He hobbled slowly, carefully, out of the door and across the level grass toward the hillside. He did not pause to wonder why no one followed him down to see if he was badly hurt.

Iris Murdoch, *The Book and the Brotherhood*
New York, Viking Penguin Inc., 1988, p. 91

Infantile Glaucoma in Down's Syndrome (Trisomy 21)

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We examined five patients with Down's syndrome and bilateral infantile glaucoma. In the first few months of life four patients had large cloudy corneas, breaks in Descemet's membrane, increased intraocular pressure, photophobia, and tearing. In one patient the diagnosis was delayed until 3½ years of age because of concomitant nasolacrimal duct obstruction. Two patients developed cataracts and retinal detachment and have undergone multiple surgical procedures. The clinical course in these two older patients suggests that coexistence of congenital glaucoma, severe myopia, and cataracts in patients with trisomy 21 strongly predisposes for the development of retinal detachment and poor visual outcome.

DOWN'S SYNDROME is the most common viable autosomal trisomic syndrome.[1] Overall incidence is about one in 600 to 800 live births, with 11,000 new cases per year in the United States. The risk of having a child with trisomy 21 increases with increasing maternal age. Trisomy of chromosome 21 resulting from nondisjunction during the meiotic process is by far the most common cytogenetic type (95% of cases), followed by translocation of the long arm of chromosome 21 to one of the acrocentric chromosomes in 4% of cases, and mosaicism in 1% of cases. The main phenotypic features include hypotonia, short stature, mental retardation, a brachycephalic head with a flat occiput, mongoloid slanting of the eyelid fissures with epicanthus, low bridge of the nose, protruding large tongue, short and broad hands with simian creases, incurving of the fifth digits, and characteristic dermatoglyphic patterns. One third of patients have congenital heart disease. Patients with Down's syndrome are at 15 times increased risk of developing leukemia. Major and minor ocular abnormalities are associated with trisomy 21 and include, in decreasing frequency of occurrence, upward-slanted, almond-shaped palpebral fissures; Brushfield spots in light irides; blepharitis; Brushfield spots in dark irides; cataracts; strabismus; myopia of more than 4 diopters; nystagmus; keratoconus; and retinal detachment.[2-11] Rarely reported ocular findings include ectropion, optic atrophy, nasolacrimal duct obstruction, retinoblastoma, and tapetoretinal degeneration.[2-11] Infantile glaucoma has only previously been described in six patients with Down's syndrome.[7,11] Herein we describe five patients with trisomy 21 and infantile glaucoma.

Case Reports

Case 1

A 20-year-old woman with Down's syndrome was first seen at age 3½ years because of tearing, photophobia, redness, recurrent sties, and blepharoconjunctivitis. She had been treated for nonpatent nasolacrimal ducts with multiple probing procedures. Ocular examination under anesthesia at that time showed horizontal corneal diameters of R.E.: 13.5 mm and L.E.: 13 mm. Breaks in Descemet's membrane were evident in both eyes. Intraocular pressure was increased. The anterior chambers were deep, there were numerous Brushfield spots, and the lenses were clear. The refractive error was R.E.: −16.00 diopters and L.E.: −17.00 diopters. Goniotomies were performed in the nasal quadrants of each eye. Initially, therapy was successful, with a decrease in symptoms and intraocular pressure. Two months postoperatively, tearing recurred in the right eye and two nasolacrimal duct probings and excision of a right upper eyelid chalazion were performed.

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Six months postoperatively, there was an increase in intraocular pressure in both eyes. Goniotomies were repeated at 5 years of age. Subsequent examinations were significant for the development of neovascularization of the peripheral cornea and the development of keratoconus in both eyes. A retinal detachment in the right eye was noted at 8 years of age, and a dense posterior subcortical cataract developed one year later. A scleral buckling procedure and aspiration of the cataract with a basal iridectomy were performed. Cyclocryotherapy of the inferior half of the ciliary body was performed in the left eye at age 10 years for a refractory intraocular pressure increase. Follow-up examinations over the next ten years showed persistently increased pressure and progressive ectasia of the left cornea, with an episode of hydrops at age 17 years. In 1985, epikeratophakia was attempted on the right eye, with subsequent removal of the lenticule because of graft infection.

On examination at 20 years of age (Fig. 1), the cornea in the right eye was vascularized peripherally with central corneal haze, and a deep anterior chamber and horizontal breaks in Descemet's membrane were present. The pupil was slightly irregular, measuring 5 to 6 mm in diameter. The vertical and horizontal corneal diameters measured 15 mm and 16 mm, respectively. Intraocular pressure was 43 mm Hg. The retina was detached and there were several retinal holes in the posterior pole. In the left eye there was complete corneal vascularization, with central dense white thickening and scarring. The corneal diameter was 15 mm and intraocular pressure was 50 mm Hg. There was marked perilimbal injection and the anterior chamber was deep. The fundus could not be visualized. Cyclocryotherapy was performed on the nasal half of each eye without complications.



Fig. 1 (Traboulsi and associates). Patient 1 at age 20 years. Note bilateral ectatic and enlarged corneas. The right cornea is severely opacified.

Case 2

A 16-year-old girl, one of monozygotic twins with Down's syndrome, was initially seen at age 4 months because of tearing, corneal haze, and buphthalmos, which was more prominent in the left eye. Ocular examination at that time disclosed a moderately hazy cornea in the left eye, with three transverse irregular linear markings extending across the entire cornea in the horizontal meridian. In the right eye there was minimal corneal haze. The horizontal corneal diameters were R.E.: 12.50 mm and L.E.: 12.00 mm. Intraocular pressure as measured by Drager applanation tonometry was R.E.: 11 mm Hg and L.E.: 13 mm Hg. The anterior chambers were moderately deep and Brushfield spots were present in both eyes. Ophthalmoscopy disclosed sharp pink optic disks without significant cupping.

One month later, intraocular pressure was repeatedly measured to be 30 to 37 mm Hg in each eye and goniotomies were performed on both eyes. At surgery, a fine translucent membrane was found overlying the trabecular area and extending from the base of the iris up to Schwalbe's line. A similar-appearing membrane was present in the right eye, with dense white dentate projections into the base of the iris from the trabecular meshwork area.

At age 14 months intraocular pressure was normal, and there was no corneal haze. Retinoscopy at 3½ years of age showed a severe myopia of R.E.: −15.00 diopters and L.E.: −20.00 diopters and severe astigmatism (R.E.: 5.00 diopters and L.E.: 4.00 diopters) that were corrected by spectacles.

At age 5 years, the patient underwent aspiration of cataracts in both eyes. Discission of a secondary membrane was required in the right eye. Four months later, an anterior vitrectomy and sector iridectomy were performed on the left eye for pupillary block. Examination at 7 and 8 years of age showed evidence of recurrent intraocular hemorrhages resulting from self-inflicted injuries. The final outcome was an atrophied, blind left eye.

At age 10 years, the patient was found to have a total retinal detachment with dialysis and extensive vitreous traction in the right eye. A scleral buckling procedure and vitrectomy

were performed with good initial surgical results. The retina subsequently redetached. A pars plana vitrectomy, membrane stripping, and revision of the scleral buckle were performed but were not successful in reattaching the retina. No further surgery was attempted.

The patient at present has no useful vision and is enrolled in a residential school for the blind. The twin sister did not have infantile glaucoma and did not have severe systemic and developmental affliction with Down's syndrome.

Case 3

A 13-month-old boy with Down's syndrome (Fig. 2) was seen because of tearing and light intolerance. On examination he had central, steady, and maintained vision in each eye. Intraocular pressure measured 24 to 30 mm Hg in each eye on repeated occasions. Horizontal corneal diameters were R.E.: 13.5 mm and L.E.: 14 mm and horizontal breaks in Descemet's membrane as well as Brushfield spots were present bilaterally. Pupillary reactions were normal. Retinoscopy demonstrated errors of refraction of R.E.: −10.00 diopters and L.E.: −9.50 +2.50 × 180. On ophthalmoscopy the disks were pink and sharp with cup-to-disk ratios of R.E.: 0.5 and L.E.: 0.4; the retinal vessels were slightly tortuous. He underwent bilateral trabeculotomies ab externo with good postoperative intraocular pressure control at two years of follow-up.

Case 4

A 6-week-old boy with Down's syndrome was examined for excessive tearing from his right eye. There was no photophobia. On ocular examination the corneal diameters were R.E.: 12.0 mm and L.E.: 12.5 mm. The left cornea was slightly hazy, but there were no breaks in Descemet's membrane. Cycloplegic refraction was +2.75 diopters in each eye. The cup-to-disk ratio measured 0.2 in each eye. Intraocular pressure was R.E.: 12 mm Hg and L.E.: 13 mm Hg.

The child returned at age 5 months after his mother noticed an enlargement of his corneas. Intraocular pressure was R.E.: 25 mm Hg and L.E.: 35 mm Hg. Cycloplegic refraction was R.E.: +0.75 diopters and L.E.: plano. The cup-to-disk ratio had increased to 0.35 in each eye. Goniotomy was performed on both eyes and intraocular pressure returned to normal. After surgery the cup-to-disk ratio decreased to 0.1 in each eye and cycloplegic refraction increased to R.E.: +2.00 diopters and L.E.: +1.50 diopters.

Examination at age 3 years showed central, steady, and maintained vision in each eye, and intraocular pressures of 10 mm Hg in each eye. Refraction, corneal diameters, and cup-to-disk ratios were unchanged.

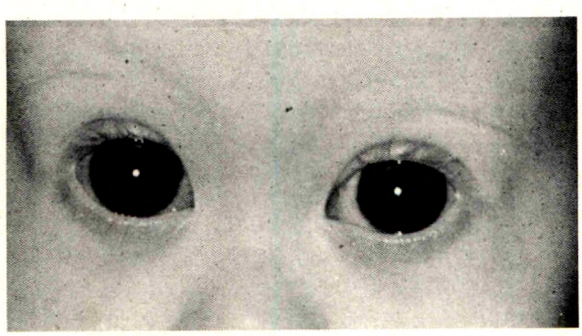


Fig. 2 (Traboulsi and associates). Patient 3 at age 2 years. Note large corneal diameters and typical palpebral features of Down's syndrome. Brushfield spots are also present.

Case 5

A 4-month-old boy with Down's syndrome was examined for corneal haze in the right eye. Corneal diameters were R.E.: 13 mm and L.E.: 12.5 mm. Both corneas were mildly hazy and horizontal breaks in Descemet's membrane were present bilaterally. Intraocular pressure was between 30 and 40 mm Hg in each eye. The cup-to-disk ratio was 0.4 in each eye. Goniotomies were performed on both eyes and intraocular pressure returned to normal. Two weeks postoperatively retinoscopy became possible and cycloplegic refraction was R.E.: −9.25 and L.E.: plano. The infant objected to occlusion of the left eye. There was no strabismus. Glasses were prescribed with part-time occlusion of the left eye. Visual acuity improved in the right eye over several months. At age 9 months, refraction was R.E.: −11.00 +4.00 × 100 and L.E.: −3.50 +1.50 × 180. Intraocular pressure was 12 mm Hg in each eye. The cup-to-disk ratio had decreased to 0.3 in each eye.

Examination at the most recent visit at age 3½ years showed clear corneas; central, steady, and maintained vision bilaterally; and an unchanged refraction. Intraocular pressure was 12 mm Hg in each eye and the cup-to-disk ratio was R.E.: 0.3 and L.E.: 0.2.

Discussion

Our patients manifest most of the ocular abnormalities of Down's syndrome, including some of the less common ones such as keratoconus, retinal detachment, infantile glaucoma, and nasolacrimal duct obstruction. In Patient 1, chronic blepharoconjunctivitis and impatent nasolacrimal ducts contributed to the delayed diagnosis of congenital glaucoma. Nasolacrimal duct obstruction is a rare finding in trisomy 21.[8] Patient 1 also developed keratoconus at age 7 years. Keratoconus occurs in 5.5% to 15% of patients with Down's syndrome[3,5,10] and is believed to be caused by increased eye rubbing secondary to irritation from blepharitis or by an inherent defect in the biochemical structure of the cornea.[10] The acute form of keratoconus is rare in Down's syndrome.[6,12] Acute hydrops was diagnosed in Patient 1 at age 18 years and increased intraocular pressure may have contributed to its development. Intraocular pressure measurements were not reported in the articles by Slusher, Laibson, and Mulberger,[6] or Kenyon and Kidwell.[12]

Infantile glaucoma has seldom been reported in association with Down's syndrome. François, Berser, and Saraux[7] observed one case among 67 patients studied, and cite a communication from Lejeune who found four such cases in a series of 2,200 patients with trisomy 21. Several investigators[2,9,10] who have studied large numbers of Down's syndrome patients did not report concomitant congenital glaucoma. However, it is uncertain whether intraocular pressure was routinely measured in these patients. Bardelli, Hadjistilianou, and Trezzotti[11] reported one case of infantile glaucoma in Down's syndrome. Another patient was described who had trisomy 21 and infantile glaucoma in a family where Rieger's anomaly was present in three generations on the patient's paternal side.[13] That infant was found to have increased intraocular pressure and an annular adhesion of iris stroma to the posterior corneal surface, consistent with Rieger's anomaly. In Patient 2 a translucent membrane with white fibrous strands was observed over the anterior chamber angle, but there were no iris strands to an anteriorly displaced Schwalbe's line as occurs in anterior segment dysgenesis. The presence of corneal edema in a patient with Down's syndrome, even in the presence of keratoconus, should alert the ophthalmologist to the possibility of undiagnosed glaucoma and intraocular pressure should be measured.

Four of our patients have severe myopia, and two developed retinal detachments and cataracts that required multiple surgical procedures, eventually leading to loss of vision and phthisis bulbi. The relative roles of cataract surgery and severe myopia in the origin of retinal detachments in these cases is not clear, nor is the role of increased intraocular pressure as a possible cause of the severe myopia. In Patient 2 retinal detachment preceded cataract extraction, whereas it followed cataract surgery in Patient 1. The combination of infantile glaucoma, severe myopia, and cataract in patients with Down's syndrome appears to be an important risk factor for poor visual outcome. Mentally retarded patients constantly rub their eyes and self-inflicted ocular injuries with intraocular hemorrhage can result, as was seen in Patient 2. Protective eye gear is indicated in these patients before and after ocular surgery.

Primary infantile glaucoma has been considered by some to be a single autosomal recessive gene disorder. Detailed genetic studies using segregation and family analysis suggest a mixture of recessive, dominant, multifactorial, and sporadic cases.[14] Merin and Morin,[15] in a study of 64 families, concluded that monogenic inheritance of infantile glaucoma is unlikely and that this disease is probably polygenic or multifactorial. Another study of 126 families from Czechoslovakia[16] indicated that in the nongypsy population inheritance of congenital glaucoma is probably multifactorial, while in the gypsy population the disease follows an autosomal recessive inheritance pattern with complete penetrance. The occurrence of infantile glaucoma in only one of monozygotic twins, both with trisomy 21 (Patient 2 in the present study), supports the likelihood of polygenic inheritance in some cases.

Other chromosomal aberrations have also been reported in association with infantile glaucoma and add further evidence to the heterogeneous origin of this condition.[7,12,13,17-33] Increases in intraocular pressure in these patients is probably the result of a developmental defect of the anterior chamber angle. Histologic study of one case of infantile glaucoma and a chromosomal abnormality by Broughton, Fine, and Zimmerman[23] showed bridging strands or pillars of trabecular tissue, which were morpho-

logically similar to the adjacent uveal meshwork, that originated in the anterior border of the iris root and inserted along the uveal meshwork. These findings are similar to the gonioscopic findings in our Patient 2. In addition to these strands that formed a discontinuous bridging network across the angle, Broughton, Fine, and Zimmerman[23] found a compacted trabecular meshwork closing both intertrabecular and transtrabecular spaces. In another case, Reardon and coworkers[19] found no histologically identifiable trabecular meshwork or canal of Schlemm. Yanoff, Rorke, and Niederer[34] postulate that ocular development is not controlled by a single chromosome or region of a chromosome, since similar anomalies have been reported with different chromosomal aberrations, as well as with normal chromosomes. The association of Down's syndrome and infantile glaucoma adds further evidence to the genetic heterogeneity of the latter disease.

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OPHTHALMIC MINIATURE

"Hugh, bring the *Examiner* along with you."

It was spread open across the chair in which I used spend my evenings, near the fire, and the page upon which my eye fell had an unfamiliar look to it, column beside column of the one account, with some of the paragraphs set in heavier type than the others. I took my spectacle case from my breast pocket, and fastened my spectacles upon my head. One of the bold paragraphs swam into my cleared vision, like a fish darting from murky water to the clear glass wall of its tank.

Thomas Flanagan, *The Tenants of Time*
New York, E. P. Dutton, 1988, p. 121

Effects of Argon Laser Iridotomy on the Corneal Endothelium

William C. Panek, M.D., David A. Lee, M.D., and Robert E. Christensen, M.D.

We studied 14 eyes of 14 patients undergoing argon laser peripheral iridotomy for occludable (narrow) anterior chamber angles. Preoperative and postoperative pachymetry and corneal endothelial cell counts by specular microscopy were obtained centrally and in both the treated and nontreated superior quadrants. No significant differences were found between preoperative and postoperative measurements of corneal thickness and endothelial cell counts in any area.

ARGON LASER peripheral iridotomy is a common treatment for angle-closure glaucoma. Numerous clinical studies attest to the efficacy of this procedure in producing a patent peripheral iridotomy and alleviating pupillary block.[1-7] Long-term analysis of results indicates that no significant sight-threatening complications are associated with this procedure.[8,9] Short-term corneal insult secondary to the argon laser, recognized by both clinicians and researchers, is often referred to as corneal burns of the epithelium and endothelium.[2,6,10] The clinical importance of these corneal changes is questionable, with human and animal studies giving variable data. We report herein the results of a prospective study using specular microscopy to define endothelial cell counts in treated and untreated quadrants, before and after argon laser iridotomy.

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Patients and Methods

Fourteen patients (19 eyes) were enrolled in this study. All eyes had either chronic narrow-angle glaucoma or were fellow eyes of an eye with angle-closure glaucoma. Eyes with previous corneal endothelial disease or eyes that had an angle-closure glaucoma attack were excluded from the study to allow unbiased evaluation of the argon laser effect on clinically normal endothelium. A complete ocular examination including slit-lamp biomicroscopy, tonometry, gonioscopy, ophthalmoscopy, and visual field examination was performed on each patient.

All procedures were performed at our institution. Before treatment, one drop of proparacaine hydrochloride 0.5% was administered and an Abraham goniolens with methylcellulose was placed on the surface of the eye. A blue-green argon laser was used. An average of 104 burns (S.D., 54.8) of 50-μm spot size, ranging in power from 400 to 1,000 mW, and ranging in duration from 0.1 to 0.5 second were used to obtain a patent iridotomy in all eyes. All treatments were given to the superotemporal quadrant of the peripheral iris. There were no complications during the laser procedure.

Preoperative corneal pachymetry and cell counts were obtained centrally, in the treated superotemporal quadrant, and in the nontreated superonasal quadrant. A specular microscope was used in conjunction with a video recording system. After careful focusing, the cells were recorded and counted off of videotape. All pachymetry was performed with the same machine. The measurements were repeated in the same locations between one and eight weeks postoperatively.

Comparisons of corneal status were made before and after laser treatment of the treated

site as well as between treated and nontreated areas. To eliminate bias, only one randomly selected, treated eye from each patient was included in the final statistical analysis, for a total of 14 study eyes. Student's paired *t*-test and the paired Wilcoxon test were used. $P < .05$ was considered statistically significant.

Results

No significant differences were detected between preoperative and postoperative pachymetry and endothelial cell counts, at any of the three sites (Table). The normal range of corneal endothelial cells in our laboratory is 2,000 to 4,000 cells/mm^2. All of the subjects in this study were within the normal range. No significant difference was detected when comparing preoperative and postoperative corneal endothelial cell counts and corneal thicknesses between the treated site and the nontreated sites.

Statistical power calculations for paired *t*-tests showed that we can be 90% confident that our sample size of 14 eyes would produce a significant *t*-test result if the true mean difference is at least 200 cells/mm^2 in cell count or at least 0.02 mm in corneal thickness.[11] These differences fall within the reproducible range of the instruments used.

TABLE
PREOPERATIVE AND POSTOPERATIVE PACHYMETRY AND ENDOTHELIAL CELL DENSITY
(N = 14)

SITE	MEAN ± S.D. CORNEAL THICKNESS (MM)	MEAN ± S.D. CELL DENSITY (CELLS/MM^2)
Untreated central site		
Preoperative	0.54 ± 0.02	2,407 ± 334
Postoperative	0.54 ± 0.02	2,385 ± 289
Treated superotemporal site		
Preoperative	0.57 ± 0.03	2,429 ± 300
Postoperative	0.58 ± 0.03	2,400 ± 283
Untreated superonasal site		
Preoperative	0.57 ± 0.03	2,442 ± 262
Postoperative	0.58 ± 0.03	2,392 ± 259

Discussion

Argon laser peripheral iridotomy can be used safely and effectively to treat angle-closure glaucoma.[1-9] Possible complications, usually short term, include blurred vision, pupillary distortion, ocular irritation and inflammation, inability to produce an iridotomy, hemorrhage, secondary closure of the iridotomy, focal lens opacities, transient increase in intraocular pressure, and corneal burns.[10]

The observed changes in the cornea have been well documented clinically; however, their long-term clinical importance is uncertain.[12-15] Eyes that have suffered an angle-closure glaucoma attack have been shown to have a significantly reduced number of corneal endothelial cells.[16] This phenomenon, believed to be secondary to marked pressure increase during the attack, could place these eyes at a greater risk for corneal decompensation should the laser iridotomy cause further significant endothelial cell damage.

Animal studies indicate that little damage occurs to the corneal endothelium after argon laser iridotomy. Hirst and associates[12] performed iridotomies on nine cynomolgus monkeys and studied the effect on the endothelium for 31 days postoperatively using scanning electron microscopy. No significant changes occurred.

Results of human studies have been variable. Robin and Pollack[7] reported an 8% ± 7% decrease in central endothelial cell counts after argon laser iridotomy compared to a 0% ± 5% decrease after Nd:YAG laser iridotomy ($P < .01$). Hong, Kitazawa, and Tanishima[13] also demonstrated endothelial damage after argon laser iridotomy, manifested by an increase in mean central corneal endothelial cell size noted three months after the procedure.

Other investigators have reported no significant effect from laser iridotomy on the central corneal endothelium. Smith and Whitted[14] followed up 28 eyes of 17 patients for one to 41 weeks and found no change in central endothelial cell count. Using computer-assisted morphologic analysis of central corneal endothelial specular micrographs before and after argon laser iridotomy, Thoming, Van Buskirk, and Samples[15] found no significant change in cell area, hexagonal cells, or shape factor in 14 eyes of seven patients.

We analyzed the peripheral corneal endothelium, in the same way as Hoffer and Phillippi,[17] in an attempt to document possible focal endothelial damage manifested by cell dropout or increase in corneal thickness. Using the preoperative site as well as a central and a mirror-image peripheral site as controls, we found no significant change in the central and peripheral corneal endothelial cell count or corneal thickness after argon laser iridotomy, with a follow-up period of one to eight weeks.

Possible reasons for not being able to detect a difference include placement of the specular microscope probe in a region adjacent to the area of actual damage, an inadequate number of treated eyes, or that argon laser iridotomy damage to the corneal endothelium was not detectable by specular microscopy. Statistical analysis showed that with our population size of 14 eyes, we had a 90% chance of detecting a difference of 200 cells/mm^2. Thus, it appears that no significant acute damage from argon laser iridotomy can be detected by loss of corneal endothelial cells or increase in corneal thickness. This demonstration of short-term safety to the corneal endothelium should be noted when considering the benefits vs possible risks of argon laser iridotomy in borderline cases (for example, eyes with occludable angles without a history of angle-closure attacks).

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Ferrous Intraocular Foreign Bodies and Magnetic Resonance Imaging

Syd Williams, M.D., Devron H. Char, M.D., William P. Dillon, M.D., Nora Lincoff, and Michael Moseley, Ph.D.

We placed various sized ferrous foreign bodies in and around the eye, sclera, and orbit in a rabbit model before performing magnetic resonance imaging studies. All foreign bodies were detected on plain x-rays. Only one of the largest fragments (3 × 1 × 1 mm) demonstrated movement on exposure to the magnetic field.

MAGNETIC RESONANCE IMAGING is the radiologic imaging study of choice for many central nervous system diseases. It is especially useful in the evaluation of demyelinating diseases or lesions of the cerebellum or brainstem. Magnetic resonance imaging does not expose patients to ionizing radiation. However, the biologic hazards of a powerful magnetic field are not well delineated. An anecdotal report of sudden blindness secondary to a vitreous hemorrhage from an occult intraocular foreign body increased realization of potential occupational risk factors.[1] This case resulted in the general exclusion of steel workers, pipefitters, welders, and other patients with a history of metal work from undergoing magnetic resonance imaging studies.

We used a rabbit model to examine the consequences of magnetic resonance imaging in the presence of various sized ferromagnetic foreign bodies of the cornea, conjunctiva, sclera, vitreous, and orbit. These data demonstrate that the broad exclusionary criteria are probably unwarranted. We devised a new set of guidelines for patients with possible occult ocular or adnexal metal foreign bodies who require magnetic resonance imaging studies.

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From the Departments of Ophthalmology (Drs. Williams, Char, and Lincoff) and Radiology (Drs. Dillon and Moseley), the University of California, San Francisco. This study was supported in part by an unrestricted grant from That Man May See, the Beal Foundation, Richard and Gail Siegal, and American Cancer Society grant PDT 321.

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Material and Methods

We placed ferromagnetic steel fragments in or around 18 eyes of nine New Zealand white rabbits under ketamine anesthesia. The fragments ranged in size from 0.1 × 0.1 × 0.1 mm to 3 × 1 × 1 mm (Table). The fragments all consisted of steel shavings and filings. Metal fragments were placed subconjunctivally in two rabbits and on the conjunctival surface in the upper and lower fornices of one rabbit. Intrascleral objects were placed in a midscleral lamellar pocket 3 to 4 mm posterior to the corneoscleral limbus. The intracorneal foreign bodies were placed in a stromal pocket. The orbital foreign bodies were placed about 1 cm posterior to the equator of the globe through the superior and inferior fornices, respectively. Intravitreal foreign bodies were placed in the midvitreous, posterior to the lens after a sharp incision was made with a myringotomy blade. Indirect ophthalmoscopy was performed to assess intraocular position and trauma from the foreign body placement before exposure to the magnet.

All animals were studied under general anesthesia. Orthogonal plane roentgenograms were used to localize foreign bodies before and after magnetic exposure. The animals were positioned prone and then placed into a 2.0-T superconductive unit for 15 minutes. The rate of insertion into and removal from the magnet was approximately 12 inches per second. Four rabbits were also imaged with 5.0-mm coronal sections (repetition time, 400 msec; echo time, 20 msec). The rabbits were examined clinically and with indirect ophthalmoscopy immediately after exposure. Two eyes with intravitreal for-

TABLE
SIZE AND DISTRIBUTION OF FERROMAGNETIC FRAGMENTS

EYE NO.	LOCATION	SIZE (MM)	MAGNETIC RESONANCE IMAGING PERFORMED*	EVIDENCE OF FOREIGN BODY MOVEMENT	
				CLINICAL	RADIOLOGIC
1	Superior fornix	0.5 × 0.5 × 0.1	No	No	No
2	Superior fornix	Four filings, 0.5 to 1.5 mm greatest diameter	No	No	No
3	Inferior fornix	Four filings, 0.5 to 1.5 mm greatest diameter	No	No	No
4	Cornea	0.1 × 0.1 × 0.1	No	No	No
5	Cornea	0.1 × 0.3 × 0.5	Yes	No	No
6	Cornea	0.5 × 0.5 × 0.1	No	No	No
7	Cornea	0.3 × 0.2 × 0.2	Yes	No	No
8	Subtenon	0.5 × 0.2 × 0.1	No	No	No
9	Sclera	0.7 × .05 × .05	No	No	No
10	Sclera	0.5 × 0.2 × 0.1	No	No	No
11	Vitreous	3.0 longest dimension	Yes	No	No
12	Vitreous	3.0 longest dimension	Yes	No	No
13	Vitreous	2.0 longest dimension	Yes	No	No
14	Vitreous	3.0 longest dimension	Yes	Yes	Yes
15	Superior orbit	1.0 longest dimension	No	No	No
16	Superior orbit	1.0 longest dimension	No	No	No
17	Superior orbit	0.5 longest dimension	Yes	No	No
18	Inferior orbit	1.0 longest dimension	Yes	No	No

*Eyes that did not undergo actual magnetic resonance imaging study were exposed to a 2.0-T magnetic field for 15 minutes.

eign bodies were examined pathologically to detect subclinical damage.

Results

All foreign bodies were visible on the standard radiographic images. Magnet-induced movement of a foreign body was only demonstrated in one eye (Fig. 1). This eye contained one of the largest ferrous fragments (3 × 1 × 1 mm), which was located in the vitreous. The fragment had rotated, but caused no apparent clinical damage. One corneal foreign body was found in the fornix after exposure to the magnet; it was uncertain whether this movement was spontaneous or caused by the magnetic field. None of the other metallic fragments had demonstrable movement either on the basis of radiographic or clinical examination (Fig. 2). The metallic-induced artifact was severe in all four magnetic resonance imaging studies (Fig. 3).

Pathologic examination of the enucleated specimens showed only surgical tissue disruption at the site of object placement. No distant intraocular damage was detected.

Discussion

There is great concern about potential visual damage from movement of an inapparent intraocular ferromagnetic foreign body during magnetic resonance imaging scans. Lagouros and coworkers[2] demonstrated that intraocular ferromagnetic substances can move and cause damage; however, the size of the intraocular objects in their study was not given. In our study, using a variety of sizes and shapes of magnetic foreign bodies in and around the eye, only one large intravitreal fragment (3 × 1 × 1 mm) produced significant movement when the animal was exposed to a magnetic field similar in strength to many clinical imaging units. It is inconceivable that a mass of this size in the eye

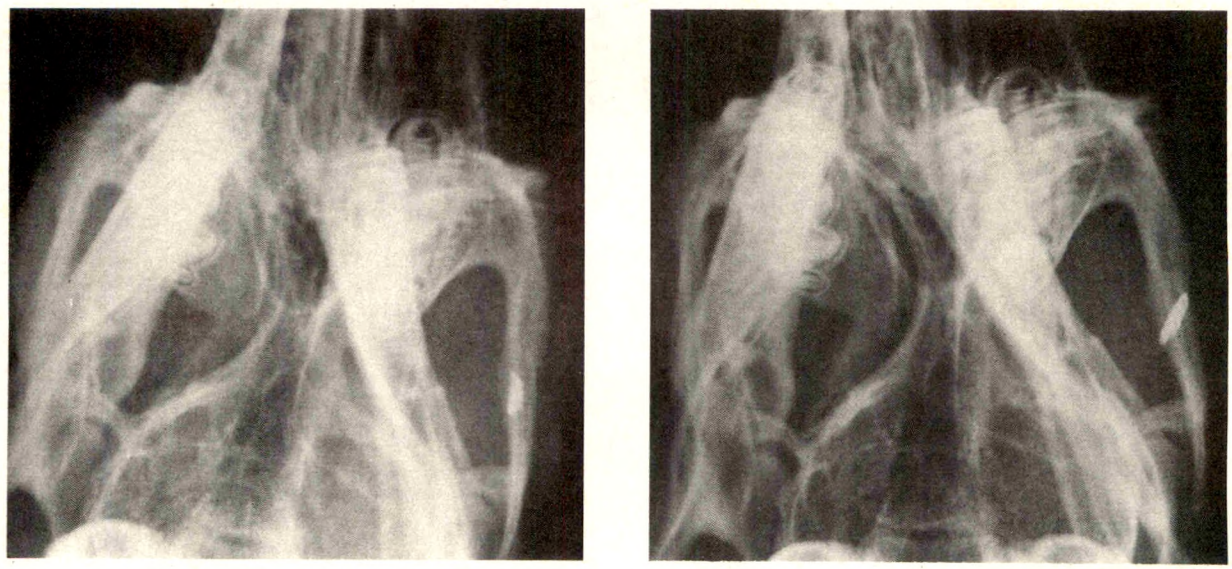


Fig. 1 (Williams and associates). Plain roentgenograms of rabbit with midvitreous 3 × 1 × 1-mm magnetic fragment. Left, Before magnetic field exposure. Right, After exposure to 2.0-T magnetic field. Note apparent movement.

would be either inapparent to the patient or the physician. We found that even tiny fragments could be imaged on routine plain x-ray, and these smaller metallic pieces neither moved nor caused significant damage as a result of magnetic resonance imaging exposure.

A relatively large amount of force is necessary to move an object through sclera or cornea, and even through semisolid vitreous gel. The force exerted on the object is dependent on its mass, composition, shape, and the strength of the magnetic field. Movement of large metal-

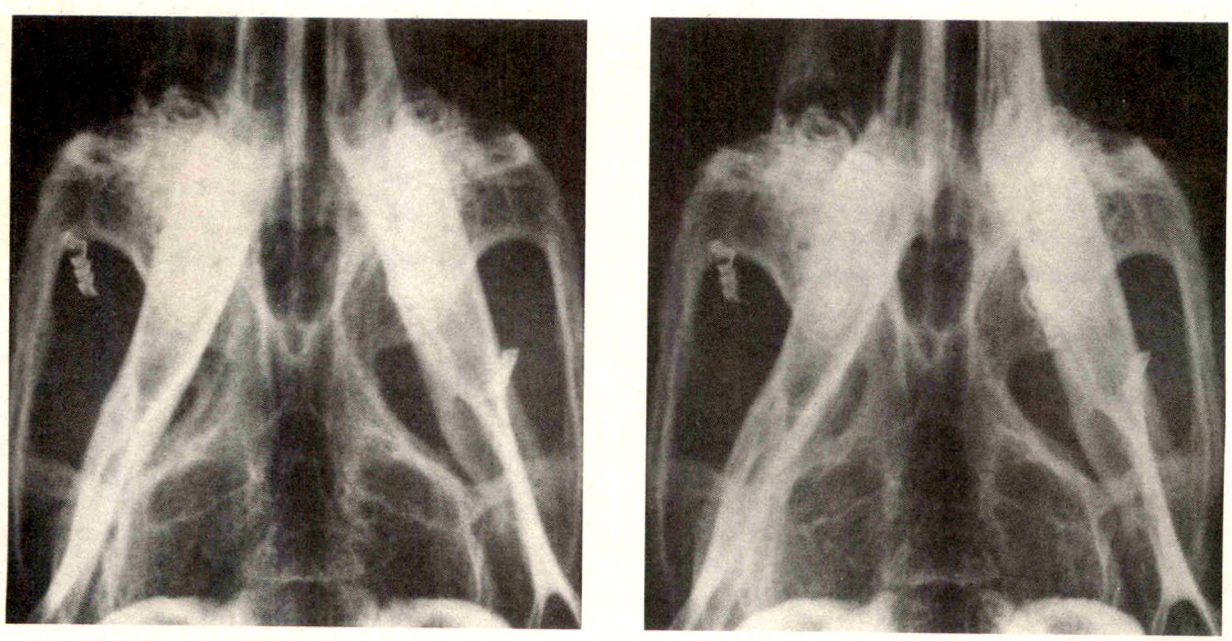


Fig. 2 (Williams and associates). Plain roentgenograms of rabbit with bilateral intravitreal metal foreign bodies 3 mm in length. Left, Before magnetic field exposure. Right, After exposure to magnetic resonance imaging. Note no change in foreign body position.

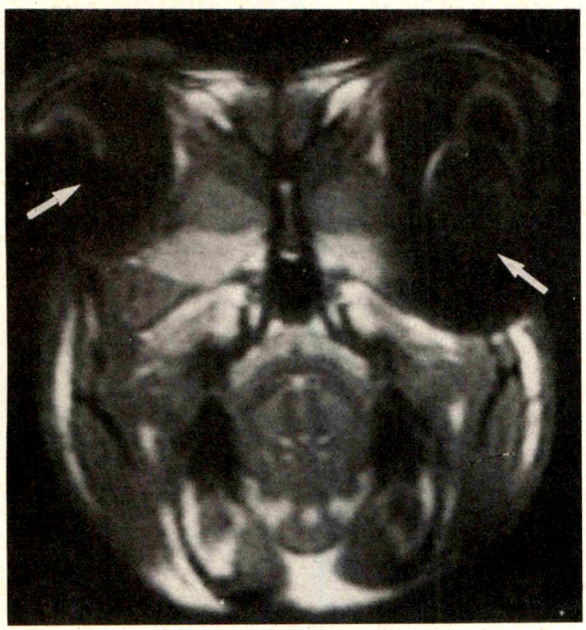


Fig. 3 (Williams and associates). Magnetic resonance imaging of rabbit shown in Figure 2, with magnetic foreign body artifact (arrows) seen in both eyes.

lic foreign objects can occur during rapid motion within the magnetic field, as occurs when a patient is moved in and out of the magnet. This produces rapid torque forces that can result in rotation of ferromagnetic objects. The previously described patient who sustained an ocular injury developed visual symptoms when being removed from the magnet.[1] Although movement of metal fragments has been demonstrated by Lagouros and associates[2] in their in vitro model, our in vivo model has shown that many small metal fragments are unaffected by standard magnetic resonance imaging. Our results demonstrate that the current exclusionary criteria of metal workers are probably too restrictive. If a metal worker has no ocular symptoms and anterior-posterior and lateral radiographs of the orbits do not demonstrate an occult foreign body, magnetic resonance imaging studies can be safely performed without intraocular or orbital damage. If ocular symptoms exist, a thorough ophthalmic examination is warranted before magnetic resonance imaging exposure.

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OPHTHALMIC MINIATURE

Her eyes, 'melted sugar eyes' one of the plausible men called them, were a disconcerting pale brown with a dark rim and blue and brown stripes leading in to the pupil, thus resembling some kind of sweetmeat.

Iris Murdoch, *The Book and the Brotherhood*
New York, Viking Penguin Inc., 1988, p. 33

Irregular Pupil Cycling as a Characteristic Abnormality in Patients With Demyelinative Optic Neuropathy

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We used an infrared videopupillometer combined with an electronic circuit that regulated the retinal light level as a function of pupil area to assess the regularity of pupil cycling in normal subjects and in patients with known abnormalities in the pupil light reflex pathways. The light stimulus was turned on whenever pupil area exceeded a preset value. Two types of abnormalities were observed for patients with demyelinative optic neuropathy: a failure of the pupil to cycle despite a preserved pupillary response to a single light pulse; and, for those patients in whom cycling was possible, a characteristic intermittent irregularity in the amplitude of pupil cycling. These abnormalities were not seen in normal subjects or in patients with ischemic optic neuropathy, surgical lesions involving the optic chiasm, Adie's syndrome, or Horner's syndrome.

Oscillations in the diameter of the pupil can be induced by focusing a small beam of light at the pupillary margin.[1,2] The average period of these oscillations has been referred to as the pupil cycle time. Measurement of the pupil cycle time has been used as a clinical method to detect dysfunction in the pupil light reflex pathways.[1-6] Although the oscillations in pupil diameter are usually regular, in some patients it can be quite irregular.[7,8] It is uncertain whether these irregularities are a result of technical difficulties in maintaining the light beam correctly focused at the pupillary margin or reflect intrinsic abnormalities in the pupil light reflex pathways. Consequently, little attention has been given to the possibility that irregularities in pupil cycling may be of diagnostic significance.

We developed an automated method for obtaining pupil cycling[9] by combining an infrared videopupillometer[10] with an electronic circuit that regulates the retinal light level as a function of pupil area; the light is turned on whenever pupil area exceeds a preset area threshold. This approach makes it easy for the patient to cooperate; is insensitive to small eye movements and the shading effects on the retina of the iris, since the light beam is focused down the center of the pupil under open loop conditions of the pupil light reflex; is not affected by segmental abnormalities in the movement of the iris, as occur in Adie's syndrome[11]; and the changes in pupil area can be recorded quantitatively as a function of time.

We used this method to examine the regularity of pupil cycling in patients with a variety of abnormalities in the pupil light reflex pathways.

Subjects and Methods

We examined 21 healthy volunteers, aged 11 to 60 years, who were free of both ocular disease and disorders known to affect autonomic function. We also examined 17 patients with abnormalities in the pupil light reflex pathways. Of these 17 patients, 13 had an afferent pupillary defect including ten with clinically definite multiple sclerosis according to the criteria of Poser and associates,[12] two with ischemic optic neuropathy, and one with

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a surgical lesion of the optic chiasm after resection of an intracranial tumor. The remaining four patients had disorders affecting the autonomic nerve supply of the pupil: three patients had Adie's syndrome and one patient had unilateral Horner's syndrome after surgical ablation of the ipsilateral superior cervical ganglion.

All measurements were performed in subjects who had been dark adapted for at least 15 minutes in a room lit only by a dim red light. During pupillary measurements, the subjects were instructed to refrain from blinking as much as possible and to fix their gaze on a target (a dim green asterisk) that appeared on a viewing screen inside the pupillometer.

Measurements of pupil area were made with an infrared videopupillometer.[10] The videocameras were a charge coupled device and their output was analyzed by a frame grabber that counted the number of pixels above a slice level (gray level) adjusted by the experimenter to discriminate between pupil and iris. The output of the frame grabber was an analogue voltage, which was proportional to the pupil area (sampling rate, 60 Hz). Light-emitting diodes provided the light source (peak wavelength, 605 nm).

Pupil cycling measurements were performed as follows.[9] The stimulating light beam of the pupillometer (diameter, 1.2 mm) was focused on the center of the pupil (diameter, 6 to 8 mm) under open loop, that is, maxwellian view, conditions. Under these conditions the iris does not alter the beam of light falling on the retina; however, we used the measured pupil area to control the timing and duration of the light pulses falling on the retina.[9,13] This was accomplished by comparing the analogue output of the pupillometer to an adjustable area threshold by using operational amplifier circuitry.[14] The output logic level goes high when the pupil area is greater than the area threshold and goes low otherwise. The high level drives the light on and illuminates the retina in open loop. In all experiments the pupil being stimulated was also the one being measured. Pupil area and the output of the photodiode were recorded as a function of time on separate channels of a chart recorder.

All measurements were performed separately on both eyes of each subject and pupil cycling was studied for at least four values of the area threshold setting to cover a pupil cycling period range of 1.5 to 5 seconds. For each threshold setting, a minimum of ten pupil cycles were obtained corresponding to 50 seconds' observation for the longest period measured. The latency time for the pupil light reflex was determined as the time between the onset of the light pulse and the onset of the pupillary constriction using a computer program incorporated in the videopupillometer. A minimum of three measurements were made for each eye.

Results

When the area threshold was set at a value larger than the initial pupil area, no regular oscillations in pupil area were seen (Fig. 1, top). However, when the area threshold was set at a value lower than the initial pupil area, repetitive constrictions and dilations in pupil area were observed (Fig. 1, middle and bottom). The light was turned on approximately 100 msec after the pupil area exceeded the area threshold. This delay represents the electronic delay in our apparatus. The onset of constriction occurred 296 ± 24 msec after the light was turned on (mean ± 1 S.D. for 21 subjects). This delay is the pupil latency time. Once pupil area constricted to a value less than the area threshold, the light was turned off after the machine delay. The pupil continued to constrict for the duration of the neural delay, after which it began to dilate.

The period and amplitude of the oscillations in pupil area depend on the value of the area threshold relative to the initial pupil area (Fig. 1, middle and bottom). This distinguishes our method from the pupil cycle time measurement.[1-6] The changes in the period and amplitude of pupil cycling as a function of the area threshold can be used to determine the rates of constriction and dilation of the pupil (unpublished data). In the present study we focused on the regularity of the amplitude of the pupil cycling.

In normal subjects, and patients with ischemic and surgical optic neuropathy and with autonomic nerve dysfunction, regular pupil cycling was obtained (Table and Fig. 2). In each case, the area threshold was adjusted to give similar values of the period of pupil cycling. There were small cycle-to-cycle variations in the amplitudes and intervals between successive constrictions, which were typically larger for patients with Adie's syndrome. Conversely, regular pupil cycling was not observed in

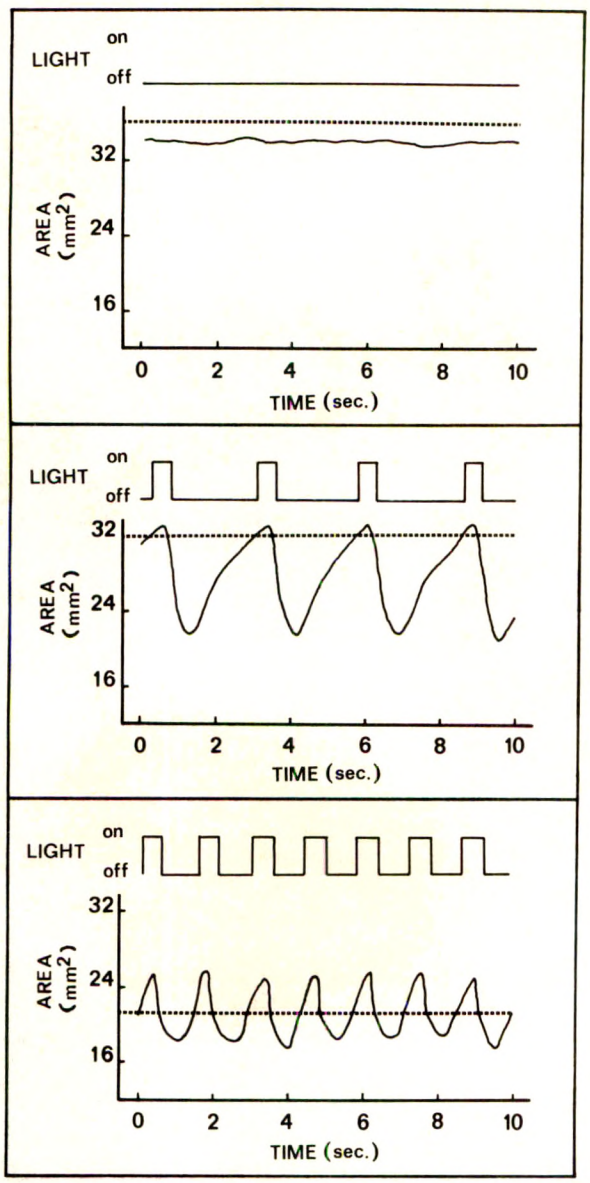


Fig. 1 (Milton and associates). Pupil cycling in a normal subject for three different values of the area threshold (dotted line). The sequence of light pulses is shown above the changes in pupil area (solid line). The pupil area before cycling was the same in all cases (approximately 34 mm^2). The initial transient changes in pupil area that occur immediately after adjustment of the area threshold are not shown (middle and bottom). They persist for the equivalent of two to three cycles.

patients with demyelinative optic neuropathy. There were two distinct types of abnormalities seen only when the light was presented to the affected eye. Of 20 eyes (ten patients) with multiple sclerosis, 16 had evidence of optic neuritis (Fig. 2). In nine of the 16 affected eyes, pupil cycling was punctuated by short segments of irregular amplitude (Patient 17, Fig. 2). These irregular segments lasted for at least the equivalent of two cycles and were characterized by their abrupt onset and offset and a marked decrease in amplitude.

We were unable to obtain pupil cycling in the remaining affected eyes. In some cases, for example, Patient 12, this was clearly because of the much reduced response of the pupil to light. In other patients, however, we were unable to maintain pupil cycling even though there was a good constriction to a single light pulse. The pupil would undergo one to two constrictions and then no further response would be seen (Patient 10, Fig. 2). A similar phenomenon occurred in some normal subjects when the area threshold was set too close to the minimum pupil area obtained in response to the light stimulus. In these cases regular cycling was restored by increasing the area threshold. However, this maneuver did not restore pupil cycling in patients with demyelinative optic neuropathy.

The latency of the pupil light reflex was prolonged for patients with demyelinative optic neuropathy (341 ± 9 msec for eight patients) compared to normal subjects (296 ± 24 msec for 17 subjects) (Student's *t*-test, $P < .05$).

Discussion

Our observations indicate that the time course for pupil cycling in patients with demyelinative optic neuropathy differs from that seen in normal subjects, patients with ischemic optic neuropathy, and patients with autonomic nerve dysfunction. There are two types of abnormalities that were observed only when light was presented to the affected eye: failure of the pupil to cycle despite a pupillary response to a single light pulse; and, for those patients in whom cycling was possible, a characteristic irregularity in the amplitude of the cycling.

Increased difficulties in obtaining sustained pupil cycling in patients with multiple sclerosis have been reported previously by several investigators using the pupil cycle time measurement.[3,7] However, it must be noted that with the use of the slit lamp to obtain pupil cycling, up to 7% of normal pupils do not cycle.[15] We experienced no difficulty in obtaining pupil cycling in normal subjects. In particular, we

TABLE
PUPIL RESPONSES IN PATIENTS WITH LESIONS IN THE PUPIL LIGHT REFLEX PATHWAYS

PATIENT NO., AGE (YRS), SEX	SINGLE LIGHT PULSE* (MM^2) RIGHT	SINGLE LIGHT PULSE* (MM^2) LEFT	PUPIL CYCLING† RIGHT	PUPIL CYCLING† LEFT	CLINICAL HISTORY
Normal subjects	12	13	Regular	Regular	—
Range	(6–20)	(6–20)			
Ischemic optic neuropathy					
1, 34, M	10	15	Regular	Regular	Right afferent pupillary defect, fat embolism, right inferior altitudinal defect
2, 55, M	7	12	Regular	Regular	Right afferent pupillary defect, temporal arteritis, right inferior arcuate defect
Optic chiasm lesion					
3, 42, F	7	10	Regular	Regular	Right afferent pupillary defect, partial resection of suprasellar meningioma, right temporal hemianopia
Horner's syndrome					
4, 14, F	10	16	Regular	Regular	Right Horner's syndrome after surgical procedure in neck
Adie's syndrome					
5, 38, F	1	8	Absent	Regular	Right Adie's pupil
6, 29, F	2	12	Regular	Regular	Right Adie's pupil
7, 36, F	6	10	Regular	Regular	Bilateral Adie's pupil, right worse than left
Demyelinative optic neuropathy‡					
8, 31, M	10	10	Regular	Irregular	Left afferent pupillary defect
9, 29, F	7	9	Irregular	Irregular	Right afferent pupillary defect, bilateral visual blurring
10, 33, F	4	7	Absent	Absent	Left afferent pupillary defect, bilateral visual blurring
11, 64, M	4	3	Irregular	Irregular	Left afferent pupillary defect, right visual blurring
12, 35, F	1	6	Absent	—	Right afferent pupillary defect
13, 19, F	3	5	Absent	Absent	Right afferent pupillary defect, visual evoked response showing bilateral slowing
14, 29, F	13	12	Regular	Irregular	Left afferent pupillary defect
15, 33, F	9	11	Irregular	Irregular	Left afferent pupillary defect, bilateral visual loss
16, 41, M	3	7	Absent	Regular	Right afferent pupillary defect
17, 29, F	9	9	Irregular	—	Right afferent pupillary defect, visual evoked response showing bilateral slowing

*Change in pupil area in response to a single 0.5-second light pulse. The intensity of the light pulse was the same for all subjects.

†Regular, pupil cycling as seen for normal eyes (see Fig. 1); irregular, irregular pupil cycling (see Patient 17, Fig. 2); absent, unable to cycle (see Patient 10, Fig. 2).

‡The clinical history gives the side of the afferent pupillary defect that was first detected clinically (range, one month to 15 years before our examination). In some patients the afferent pupillary defect was no longer detectable and in others it had switched sides, thereby indicating the presence of a new lesion.

easily elicited normal pupil cycling in two normal subjects in whom cycling could not be initiated by use of a slit lamp. Two previous studies have noted intermittent irregularities in pupil cycling of patients with multiple sclerosis[7,8]; however, the possibility that this may be specific for demyelinative lesions of the optic nerve was not recognized.

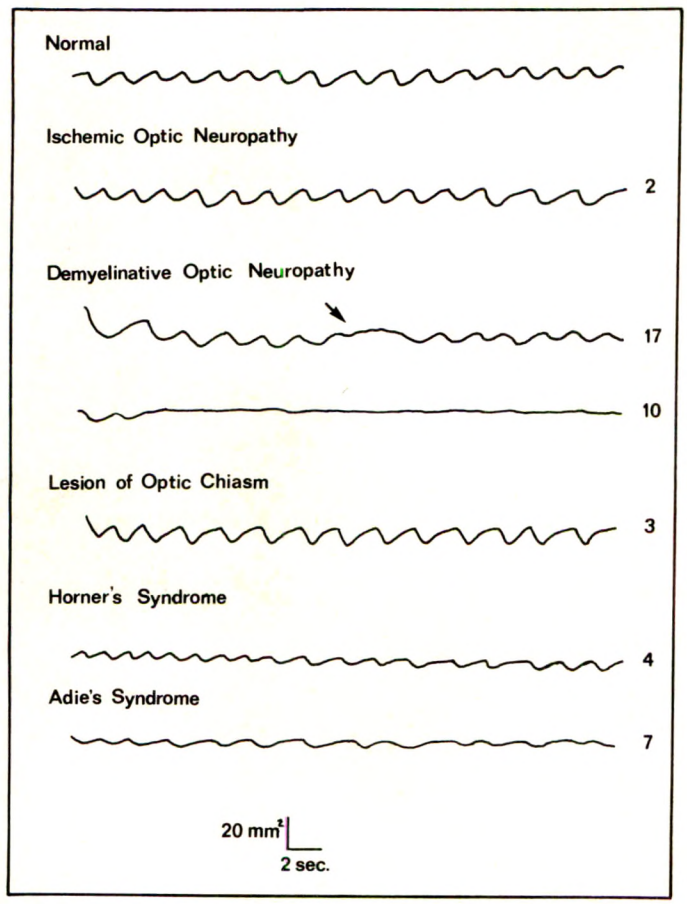


Fig. 2 (Milton and associates). Comparison of pupil cycling in a normal subject to that in patients with ischemic optic neuropathy, demyelinative optic neuropathy, Adie's syndrome, Horner's syndrome, and a patient with a surgical lesion of the optic chiasm. The numbers at the right-hand side of the figure identify the patient. The irregularity observed in pupil cycling for the patient with demyelinative optic neuropathy is indicated by the arrow.

The mechanism for the irregularities in pupil cycling in patients with demyelinative optic neuropathy is uncertain. It is unlikely that these irregularities represent pupillary fatigue, habituation, or escape,[15] since the progressive diminution of the amplitude of the pupil light reflex associated with these phenomena is not present. Additionally, pupillary fatigue typically occurs after 60 seconds,[2,15,16] whereas the irregularity in pupil cycling observed in patients with demyelinative optic neuropathy occurred within 20 seconds.

It is more likely that these irregularities are related to the prolonged latency of the pupil reflex and time-dependent afferent pupillary defects. During pupil cycling, the optic nerve transmits a repetitive train of synchronous afferent impulses as the light pulse intermittently reaches the retina. Partially demyelinated nerve fibers have difficulties in transmitting trains of impulses and undergo intermittent conduction block,[17,18] which is believed to be related to the prolongation of the refractory period for transmission.[19] Partial demyelination of even a small proportion of the optic nerve fibers may be sufficient to desynchronize the train of afferent nerve impulses[17] to the point that pupil cycling is interrupted. Conversely, in a partially infarcted optic nerve only the intact nerve fibers can conduct impulses. Since the intact fibers appear to be normally myelinated[20,21] in a partially infarcted nerve, this desynchronization should not occur and cycling should be regular. Thus, our observation that irregularities in pupil cycling are seen in optic nerves with demyelinated lesions but not in those with ischemic lesions is consistent with known differences in nerve conduction of repetitive impulses between myelinated and unmyelinated nerve fibers.

Quantitation of pupillary changes has typically been disappointing as a method for enhancing clinical acumen. For example, the demonstration of an afferent pupillary defect at the bedside is well known to be a more sensitive indicator of optic nerve dysfunction than previously reported pupillographic methods.[22] This preliminary study suggests that precise mea-

surements of pupil cycling under well-defined conditions may be useful for identifying the origin of an optic neuropathy: irregular cycling favors demyelination, whereas regular cycling favors ischemic or surgical lesions. This task is not easily accomplished by other methods.[22-24] Our method also appears to be useful for detecting whether there is bilateral optic nerve dysfunction in a patient with a relative afferent pupillary defect. Clearly, more studies involving larger numbers of patients in different stages of evolution of their disease and with comparison to other diagnostic techniques of optic nerve dysfunction, for example, visual evoked potentials, will be necessary before it will be known whether this method also has a role in detecting the presence of subclinical dysfunction in an optic nerve.

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Effects of Yellow Filter Glasses on the Results of Photopic and Scotopic Photometry

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I measured the luminosity of a white surface with seven different yellow filter glasses and a photometer with two different sensitivities, which resembled the photopic and scotopic sensitivity of a Commision Internationale d'Eclairage standard observer. When measured with filters GG 400, GG 420, GG 435, and GG 455, there was a small and almost equal reduction in the relative photopic and scotopic luminosities. Measured with filters GG 475, GG 495, and OG 515, there was a more marked reduction in the scotopic luminosities than in the photopic luminosities.

POLYMETHYLMETHACRYLATE is almost exclusively used in the production of the optic part of intraocular lenses. It is highly transparent for visible radiation, having a transmittance of 0.95 (95%) within the range of 340 to 1,100 nm.[1] To reduce the risk of retinal damage caused by ultraviolet and short wavelength blue radiation,[2] manufacturers have changed the transmittance of some intraocular lenses by adding certain chromophores to the polymethylmethacrylate. These chromophores effectively absorb ultraviolet radiation of 300 to 400 nm. Because some of the intraocular lenses made of this mixture also absorb part of the blue end of visible radiation, they have a slightly yellow tint. These intraocular lenses act like selective cutoff type, long-pass filters. According to Mainster,[3] effective protection against hazards caused by ultraviolet and short wavelength blue radiation presumes that virtually all radiation of wavelengths shorter than 430 nm will be absorbed by an intraocular lens. The use of an intraocular lens that eliminates radiation up to 450 nm,[4,5] 500 nm,[6] or even 520 nm[7] has also been suggested.

In photopic conditions, at luminosity levels higher than 10 cd/m^2, cone vision is dominant in the human eye. According to the measurements made by the Commision Internationale d'Eclairage "standard observer,"[8] the radiation of wavelength 555 nm has the highest relative photopic luminous efficiency. If a value of 1.0 is given to the relative photopic luminous efficiency of this wavelength, the value of the relative luminous efficiency will be 0.0005 for wavelengths of 400 and 730 nm.

In scotopic conditions, at luminosity levels lower than 10^{-3} cd/m^2, vision is mediated by the rods only. The highest relative scotopic luminous efficiency is produced by radiation of wavelength 510 nm.[8] Corresponding to the value of 1.0 of relative scotopic luminous efficiency for the wavelength of 510 nm, the value 0.0005 is given to the wavelengths of 380 and 650 nm. With the reduction of luminosity from the photopic to the scotopic level, the point of the spectrum with maximum luminous efficiency at 555 nm is shifted approximately 45 nm toward the shorter wavelengths to 510 mn (the Purkinje shift), the blue end of visible spectrum migrates from 400 to 380 nm, and the red end of the spectrum moves from 730 to 650 nm.

A yellow long-pass filter glass blocking the radiation of the wavelengths shorter than 480 or 510 nm has little effect on photopic luminosity.[9] This is because the radiation of shorter wavelengths has a low photopic luminous efficiency. Theoretically, in scotopic conditions the same filters are blocking a proportionally larger part of the visible spectrum as compared with photopic conditions.

The purpose of the present study was to measure the effects of yellow filter glasses on photometric results obtained by measuring the luminosity of a white surface by using a photometer with two different sensitivities, which resembled the photopic and scotopic sensitivity of a Commision Internationale d'Eclairage standard observer.

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Material and Methods

The luminance of a white barium-sulfur surface was measured with a photometer. This photometer has two different filter systems that modify the spectral sensitivity of the instrument to resemble that of a Commision Internationale d'Eclairage standard observer in photopic and scotopic conditions. The spectral sensitivity of the photometer was calibrated by the manufacturer at 10-nm intervals within the range of 380 to 750 nm. Calibration showed that there was a less than 4% difference at any location through the spectrum measured between the calibrated sensitivity as compared with the respective photopic and scotopic Commision Internationale d'Eclairage data. The calibrated relative photopic and scotopic spectral sensitivity of the photometer as a function of the wavelength is shown in Figure 1. The tops of the sensitivity curves have been artificially placed at the same height.

Seven different Schott filter glasses, 3 mm thick, were calibrated by measuring transmission with a spectrophotometer at 5-nm intervals within the range of 312 to 620 nm. The following filters were used: GG 400, GG 420, GG 435, GG 455, GG 475, GG 495, and OG 515. These Schott filters are named by the manufacturer according to the location in the spectrum of 50% transmission (the cutoff point of the filter). Calibration of these filters showed 50% transmission at the following wavelengths: 404, 420, 426, 438, 480, 497, and 510 nm, respectively. For the normal eye filter, GG 400 appears colorless, while filter GG 420 shows a slight yellow tint. The remaining five filters show a step-wise increase in yellow hue.

The photometer was directed at normal incidence to the white surface illuminated with a light source having a color temperature of 6,770 K. Each separate yellow filter glass was placed in front of the photometer and the photopic luminosity of the surface within a 3-degree area was recorded. After changing the filter system inside the photometer, the scotopic luminosity was measured in the same way. The photometer gave the readings in photopic and in scotopic units (cd/m^2).

Results

The photopic luminosity of the white surface was 9.5 cd/m^2 when measured with filter GG 400 (Table). When measured with filters GG 435, GG 455, GG 475, and GG 495 the photopic luminosity decreased from 9.0 to 8.0 cd/m^2. Measured with filter OG 515, the photopic luminosity was 7.4 cd/m^2. The relative values of the photopic luminosity gradually decreased when measured with the series of filters from 100% to 77.9%.

The scotopic luminosity of the white surface was 24.0 cd/m^2 when measured with filter GG 400 (Table). Measured with filters GG 420, GG 435, and GG 455, the scotopic luminosity decreased from 22.9 to 21.6 cd/m^2 (from 95.4% to

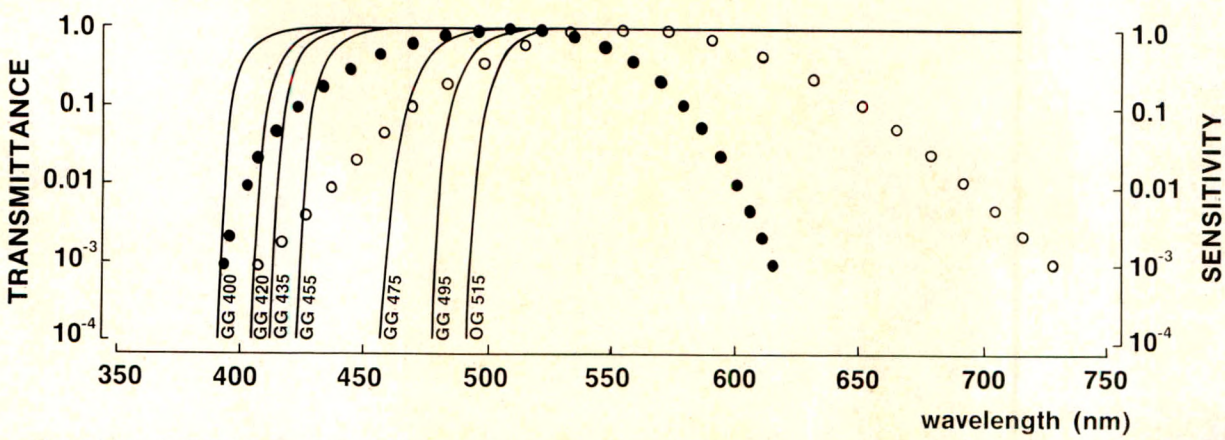


Fig. 1 (Aarnisalo). Transmittance (left ordinate, logarithmic scale) of seven yellow filter glasses as a function of wavelength. Photopic (open circles) and scotopic (closed circles) relative spectral sensitivities (right ordinate, logarithmic scale) of the photometer as a function of the wavelength are also shown. The tops of the sensitivity curves have been artificially placed at the same height.

TABLE
CHARACTERISTICS OF FILTERS AND RESULTS OF PHOTOMETRY

FILTER	CUTOFF POINT (NM)	PHOTOPIC LUMINOSITY CD/M²	PHOTOPIC LUMINOSITY %	SCOTOPIC LUMINOSITY CD/M²	SCOTOPIC LUMINOSITY %
GG 400	404	9.5	100	24.0	100
GG 420	420	9.0	94.7	22.9	95.4
GG 435	426	8.8	92.6	22.0	91.7
GG 455	438	8.8	92.6	21.6	90.0
GG 475	480	8.3	87.4	15.7	65.4
GG 495	497	8.0	84.2	11.4	47.5
OG 515	510	7.4	77.9	8.6	35.8

90.0%). Filters GG 475 and GG 495 gave the results of 15.7 cd/m² (65.4%) and 11.4 cd/m² (47.5%), respectively. Values obtained with filter OG 515 were 8.6 cd/m² and 35.8%.

The relative photopic and scotopic luminosities of the white surface measured with separate filter glasses plotted against the wavelength of the filters are shown in Figure 2. Measured with filters GG475, GG495, and OG 515, the scotopic luminosities are lower than the photopic luminosities.

Discussion

The comparison of photopic and scotopic luminosities is difficult because the same intensity of radiant energy has different luminous efficiency under photopic and scotopic conditions. A luminance of black body radiator 1 W (at 555 nm) corresponds to 680 lumen in photopic units, and 1 W (at 510 nm) corresponds to 1,745 lumen in scotopic units.[10] The ratio of these values expressed in different units (680:1,745) is 0.390. Results of the present study show that the luminosities of the white surface were 9.5 cd/m² (photopic units) and 24.0 cd/m² (scotopic units) when measured with filter GG 400 (a colorless filter). Both luminosities were produced by the same intensity of radiant energy emitted from the light source. The ratio of these values expressed in two different units (9.5:24.0) is 0.396, indicating that the photometer is well calibrated. A comparison of relative values of photopic and scotopic luminosities (in percent) does not show the same difficulty, which can be seen in the comparison of absolute values (cd/m²).

The results of the present study show that the relative scotopic luminosity of the white surface when measured with filters GG 475, GG

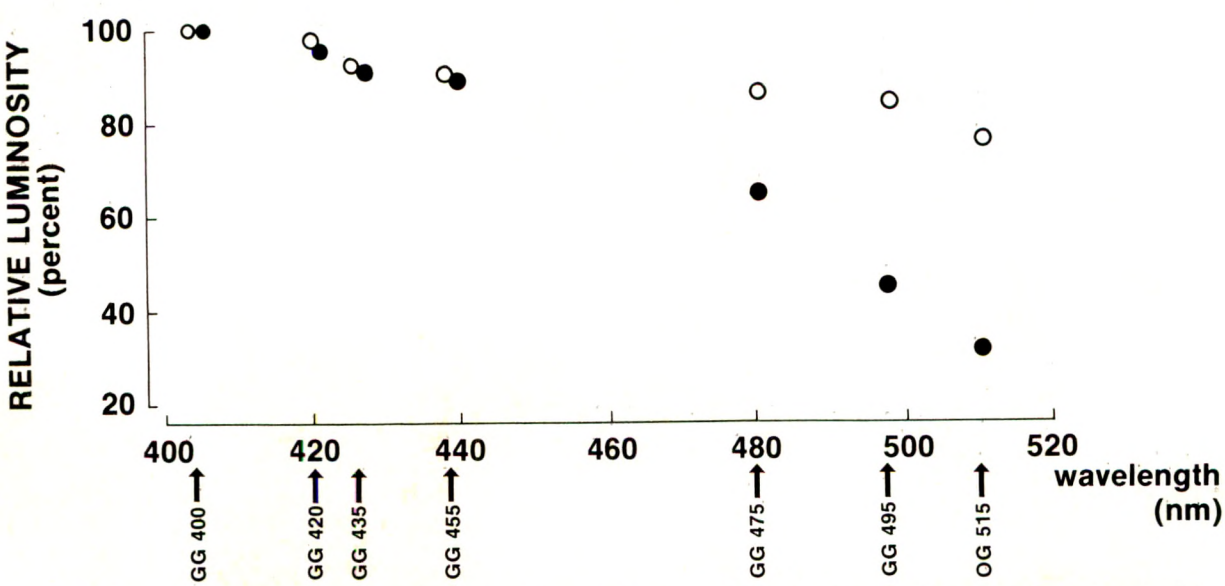


Fig. 2 (Aarnisalo). Relative photopic (open circles) and scotopic (closed circles) luminosities (in percent) of the white surface measured with seven separate yellow filter glasses plotted against the wavelength of the filters. The cutoff points are indicated by arrows. Measurements were performed with a photometer having two different sensitivities.

495, and OG 515 is much lower than the relative photopic luminosity measured with the same filters (Fig. 2). It is also evident that when measured with filters GG 400, GG 420, GG 435, and GG 455, the relative values of respective scotopic and photopic luminosities are almost equal.

Measurements in the present study were performed with a photometer with two different sensitivities. The sensitivity of a photometer cannot be related directly to the sensitivity of a human eye in photopic and in scotopic conditions. The spectral sensitivity of a photometer of high quality should closely correspond to the Commision Internationale d'Eclairage photopic or scotopic luminosity data. In any case, the Commision Internationale d'Eclairage data are considered to be approximate and do not account for the differences between various testing methods. The relative contributions of the "luminance system" and the "opponent color system" to the photopic spectral sensitivity of normal human observers should be emphasized. The variation of the results greatly depends on the testing conditions (area, duration, and illumination).[11] The shape of the top of a photopic luminosity curve shows three peaks (when tested in conditions favoring color vision).[8] Thus, a photometer with sensitivities resembling the photopic and scotopic Commision Internationale d'Eclairage data represents only a rough imitation of a human eye. Despite this inaccuracy, such a photometer can be used to demonstrate the Purkinje shift and to show the effects of yellow filters at two different illumination levels.

Absorption properties of some commercially available intraocular lenses closely resemble those of filters GG 400, GG 420, and GG 435.[3] Intraocular lenses resembling filters GG 455, GG 475, GG 495, and even OG 515 have also been recommended.[7] Cautious adaptation of the results of the present study to the physiology of human vision would suggest that an intraocular lens eliminating radiation of wavelengths shorter than 438 nm (like filter GG 455) has a small effect on photopic and scotopic luminosities. The use of an intraocular lens eliminating radiation up to 480 nm, 497 nm, or 510 nm (like filters GG 475, GG 495, and OG 515) would cause a proportionally larger decrease in relative scotopic luminosity as compared with the decrease in relative photopic luminosity. This difference is most clearly demonstrated with the use of filters GG 495 and OG 515. An intraocular lens similar to filters GG 495 and OG 515 would cause a decrease of 52.5% (GG 495) and 64.2% (OG 515) in the relative scotopic luminosity, while the respective decrease in photopic luminosity would be only 15.8% (GG 495) and 22.1% (OG 515). Such a decrease in scotopic luminosity may disturb visual functions in scotopic conditions. The use of filter GG 495 or OG 515 will cause a tritan-type color vision defect,[9,12] which clearly exceeds the normal, physiologic, mild tritanopization of color vision occurring at over 60 years of age.

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EDITORIAL

The Blood-Aqueous and Blood-Brain Barriers to Permeability

Gary D. Novack and Irving H. Leopold

The unique characteristics of the blood-aqueous barrier and the blood-brain barrier are well known. In general, these barriers prevent the transportation of certain molecules from the plasma into the eye and brain. Aqueous humor is formed by an active secretion as well as an ultrafiltration, similar to the formation of cerebrospinal fluid. The composition of the aqueous humor is much different than whole blood, plasma, or even a simple ultrafiltrate of plasma.[1,2] To describe this phenomenon of apparent active inward transport of certain substances (ascorbate and sodium) and apparent passive or active exclusion of other substances (proteins and sucrose), the concept of the blood-aqueous barrier was developed.[3]

Classic physiologic studies demonstrated that the permeability restriction of the blood-aqueous barrier, similar to the blood-brain barrier, is to exclude large molecules from the aqueous humor. Protein is present in large concentrations in the plasma, some 6,000 to 7,000 mg/100 ml. This is for the most part excluded from entry into the aqueous humor by the barrier. However, the presence of a low level of protein in the aqueous humor of normal eyes (30 to 70 mg/100 ml) demonstrates that the barrier function is not absolute. The ratio of albumin to globulin in the aqueous humor is larger than that in the plasma because of the relatively greater barrier penetration of the lower molecular weight albumin than the higher molecular weight globulins.[1,2] The function of the barrier does not appear to be related to age.[4]

Disturbance of the barrier produces well-known effects. Removal of more than 20% of the aqueous humor by paracentesis greatly increases the protein concentration in the newly formed aqueous humor.[5] In this situation, the

protein concentration can increase from approximately 30 mg/100 ml to 200 to 300 mg/100 ml, and take up to one day to return to normal concentrations.[6] Edematous ciliary processes, as observed microscopically by Greef,[7] most likely form this excess protein. The mechanism for breakdown of the blood-aqueous barrier is probably related to prostaglandin synthesis from the arachidonic acid cascade,[8-11] and the presence of other autacoids such as histamine and substance P.

A barrier disrupted by trauma produces more than a local, unilateral ocular effect. Jesner[12] found that when one cornea of a rabbit was irritated, the concentration of protein increased in the aqueous humor in both eyes. Using nitrogen mustard as the irritant, Davson and colleagues[13,14] found increased aqueous protein concentration and intraocular pressure in the eye contralateral to treatment. In pharmacologic studies of new antiglaucoma agents, contralateral decreases in intraocular pressure are often interpreted as evidence of systemic absorption.[15,16] In view of the contralateral effects that follow unilateral trauma, however, the involvement of some kind of central reflex mechanism should be considered. Given the profound contralateral effects from unilateral ocular trauma, the contralateral effects of pharmacologic ocular hypotensive agents may also involve some type of central neural reflex or humoral mechanism.[17,18]

Barrier breakdown may be measured noninvasively by following the distribution of fluorescein into the aqueous humor chamber after systemic administration, as initially described by Ehrlich.[19] Using either orally or intravenously administered fluorescein and instruments for quantifying the fluorescence in the anterior segment, the amount of fluorescein entering a postoperative eye, relative to the fellow, nonoperated on eye, can measure the extent of postoperative inflammation.[20-24] Intravenous inulin has also been used in experimental animals.[25]

Factors that change the permeability of the blood-aqueous barrier include vasoconstrictors that attenuate blood-aqueous barrier breakdown after paracentesis[26]; muscarinic agonists such as pilocarpine that increase the permeability of the barrier,[27,28] most likely by stimulation of ciliary secretory activity[2]; and inflammation, perhaps via prostaglandins,[9] which may increase the permeability of the barrier to proteins. Both corticosteroidal and noncorticosteroidal anti-inflammatory drugs, such as aspirin and indomethacin, attenuate blood-aqueous barrier breakdown in models of inflammation.[10,11,29,30] In clinical studies, treatment with topical indomethacin, flurbiprofen, or diclofenac given preoperatively and during the first few postoperative weeks decreased both the leakage of fluorescein into the anterior chamber and the clinical and biomicroscopic signs of inflammation.[20-24] Pretreatment with flurbiprofen decreased intraoperative miosis in cataract extraction procedures, and attenuated some signs of inflammation after anterior segment laser or intraocular surgical procedures.[31-40]

The integrity of the blood-aqueous barrier also changes during infection. Ocular infection alters the barrier, greatly enhancing the ocular availability of several classes of antibiotics when these are systemically administered.[41-47] This raises doubts regarding the validity of most pharmacokinetic measurements of anti-infective or anti-inflammatory agents, since these measurements are generally obtained in normal, healthy eyes,[48] whereas the agents are generally used in diseased eyes.

Recent endocrinologic research reaffirms similarities between the blood-aqueous and blood-brain barriers pointed out by Davson and Rapoport.[2,17,49] In the same way that a pathologic process in the eye may increase the permeability of the blood-aqueous barrier to proteins from the plasma, so does a pathologic process in the brain alter the blood-brain barrier function. Cohen's "law of meningitis"[50] states that substances present in the cerebrospinal fluid in concentrations greater than their concentrations in the plasma (magnesium and chloride) will decrease after barrier breakdown, whereas those present in lower concentrations relative to plasma (phosphorus, potassium, and proteins) will increase. The result is that the cerebrospinal fluid of the patient with meningitis becomes more like plasma. The sites of breakdown of blood-cerebrospinal fluid barriers are most likely the choroid plexuses, which have intracellular leaks that permit penetration of substances normally excluded from the brain.[2]

While the blood-aqueous and blood-brain barriers have many functional similarities, there are differences. For example, the vessels of the iris appear to be leakier than the vessels of the blood-brain barrier.[49] Within the eye, there are differences between the structures in the anterior chamber and those in the posterior chamber that provide barriers between the blood and the eye. In the anterior chamber, the vascular epithelium, basement membrane, and

iris stroma constitute the barrier.[1,3] In the posterior chamber, the barrier is made up of vascular endothelium and its basement membrane, stroma, and two layers of ciliary epithelium. All of these cells appear to be connected by tight junctions.[49,51] The anterior surface of the iris lacks an epithelial component. The vessels, however, by way of contrast to the ciliary region, are nonfenestrated with an unusually thick basement membrane.[1]

In addition to a barrier between the blood and the aqueous humor, there is a barrier between the blood and the posterior pole structures. This barrier consists of the ciliary epithelium (as it also faces the vitreous body), the retinal pigment epithelium, and the endothelial layer that lines retinal blood vessels. Like the blood-aqueous barrier, these cells are connected by tight junctions[49]; the retinal vessels, however, have tighter "tight junctions."[3] Histamine increases the permeability of various ocular tissue vessels, with the exception of the retina.[3] The structures of the eye are not equally permeable to substances present in the blood. The permeability and the time course of appearance of substances in the blood are much greater in the aqueous than the vitreous humor.[52,53] The vessels of the iris, in addition to being leakier than those of the blood-brain barrier, also appear to be leakier than either the ciliary or retinal vessels.[3,49] Thus, the iris may present a significant leakage point into the eye for substances from the blood, at least in the normal eye.

One might wonder what controls the development of these highly differentiated barrier tissues. While this question renains unanswered, recent research on the blood-brain barrier suggests that the development of the barrier is induced by glial, rather than neural, tissue. The structures thought to be responsible for the function of the blood-brain barrier function are the tight junctions between endothelial cells in the capillaries and venules in the central nervous system.[49,54,55] The development of such junctions is not intrinsic to the vascular cells, but appears to be induced by their environment.[56]

In a series of elegant experiments, Janzer and Raff,[56] using the anterior chamber as a body cavity available for repeated, noninvasive imaging, transplanted astrocytes from rat cerebral cortex into the anterior chambers of syngeneic rats. Within 48 hours, these implants aggregated on the iris and became vascularized. When Evans blue, a dye binding tightly to plasma proteins, was injected intravenously, these implants remained white, reflecting the integrity of the vascular-tissue barrier. When meningeal cells or fibroblasts instead of astrocytes were transplanted, no protection for vascular dye penetration was observed. These findings were also confirmed by histologic section. The authors suggest that astrocytes, but not meningeal cells or fibroblasts, can induce endothelial cells of nonnervous origin to form nonleaky vessels. They further suggest that astrocytes are responsible for the formation of the blood-brain barrier. The applicability of this theory to the blood-aqueous barrier is unknown.

The function of the blood-brain barrier may involve more than junctions. Physiologic phenomena such as hyperosmosis can induce a passive opening of the blood-brain barrier by compromising the structural integrity of the tight junctions,[49] and the delivery of agents to the brain has been enhanced by previous injections of hyperosmotic substances. In addition to the passive exclusion of agents from the blood, the blood-brain barrier also has an active nature. Agents such as essential amino acids are actively transported into the brain.[49] Pinocytosis at vascular tissues in the blood-brain barrier has been reported to be stimulated by neurohumors (norepinephrine, serotonin, and histamine), divalent ions, and trauma such as stab wounds.[49,57-59] Pinocytosis may be involved in the initiation and extension of the inflammatory demyelinating lesions in multiple sclerosis.[60] Ocular infection or surgery might also affect pinocytosis at the blood-aqueous barriers.

The integrity of the blood-aqueous barrier must be maintained to provide an appropriate environment for the ocular tissues. Alteration of the function of this barrier by trauma, surgery, or pharmacologic agents may alter the environment for these tissues. Continued work in the areas of cell membrane function, barrier physiology, and the function and treatment of barrier breakdown may enable us to understand better the development and function of the blood-aqueous barrier. We may then be able to reduce the transport into the eye of undesirable agents, such as protein, and to improve the transport of therapeutic agents into the eye. Better treatment of ocular disease may be the result.

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LETTERS TO THE JOURNAL

Bilateral Macular Holes After Nd:YAG Laser Posterior Capsulotomy

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The performance of posterior capsulotomies using Nd:YAG laser energy is widespread.[1] Although thought to be noninvasive, the procedure has been associated with a number of complications, including retinal detachment and increased intraocular pressure. Unilateral macular hole formation after Nd:YAG laser posterior capsulotomy has been reported in four patients.[2-4] We report a case of bilateral macular hole formation after Nd:YAG laser posterior capsulotomy.

A 68-year-old man underwent an uncomplicated extracapsular cataract extraction with posterior chamber lens implantation in his left eye. His history was significant for systemic hypertension controlled with chlorthalidone. Preoperative manifest refraction was −6.50 diopters. Postoperatively, the capsule was intact and best corrected visual acuity was L.E.: 20/20. Two years later, best corrected visual acuity was L.E.: 20/80, attributable to posterior capsule opacification. The patient underwent a posterior capsulotomy with 12 pulses at 1.5 mJ each from a Q-switched Nd:YAG laser delivered without a contact lens through a dilated pupil. Postoperatively, there was no increase in pressure, and a vitreous prolapse into the anterior chamber through the 4 × 4-mm capsulotomy did not occur. Best corrected visual acuity was L.E.: 20/20. Twenty-one days after Nd:YAG laser capsulotomy, the patient noted a sudden decrease in visual acuity. On examination one week later, a full-thickness macular hole (Figure) and a completely detached operculum were seen. Best corrected visual acuity was L.E.: 20/400, decreasing to counting fingers.

The patient also underwent an uncomplicated extracapsular cataract extraction with posterior chamber lens implantation in his right eye, which had a preoperative refractive error of −2.75 diopters. Postoperatively, best corrected visual acuity in the right eye was 20/20. Two years postoperatively, visual acuity had decreased to 20/60, attributable to an intact but opacified posterior capsule. Biomicroscopy disclosed an incomplete posterior vitreous separation with strand-like attachments to the macula and inferior retina, and a complete vitreous separation of the superior one third of the retina. A posterior 4 × 4-mm capsulotomy was done using 35 pulses of 0.9-mJ Q-switched Nd:YAG laser energy. Best corrected posttreatment visual acuity was R.E.: 20/20 with no vitreous prolapse noted. Ten days after the capsulotomy, the patient had a sudden decrease in central visual acuity. Results of an immediate examination disclosed a best cor-

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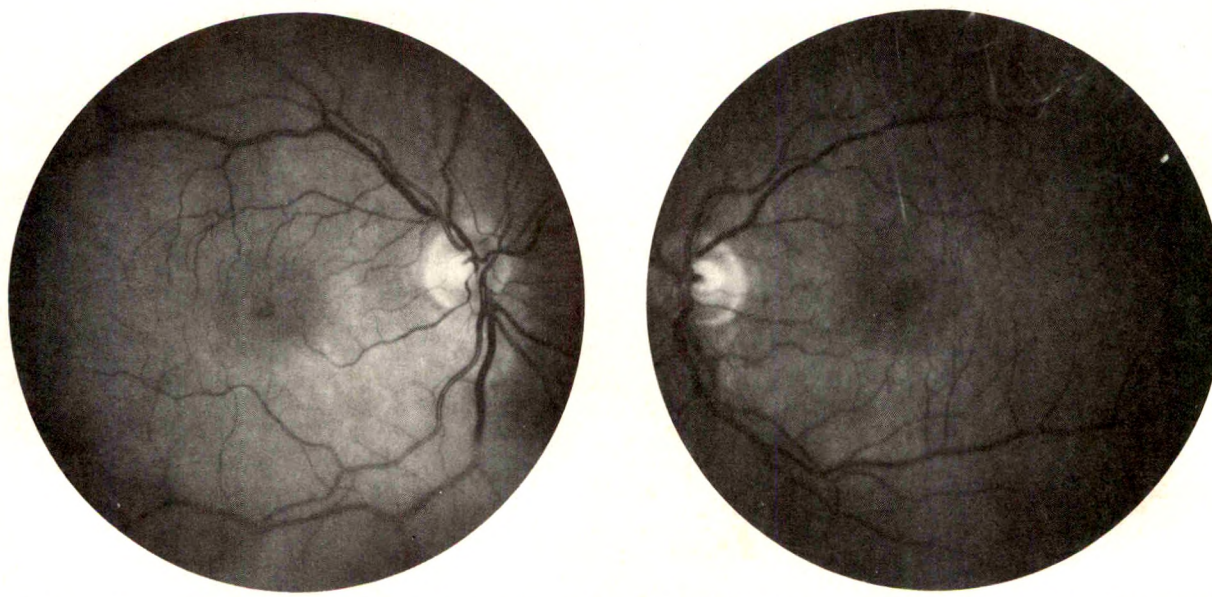


Figure (Blacharski and Newsome). Left, Fundus photograph of the right eye taken during an acute decrease in central visual acuity, from a best corrected visual acuity of 20/20 to 20/100. The patient eventually stabilized at a visual acuity of 20/200, with an estimated diameter of 350 μm and an annulus of subretinal fluid approximately 200 μm in width. Fluorescein angiography in the transit showed late staining in the area of the hole, but no window defect was noted. Right, Fundus photograph of the left eye. The horizontal diameter of the macular hole was approximately 500 μm, with an annulus of subretinal fluid 250 μm in width. This corresponded to a visual acuity of 20/400.

rected visual acuity of R.E.: 20/100, a small foveal hole (Figure), and a complete posterior vitreous separation.

Previous reports of unilateral macular hole formation documented periods usually shorter than four weeks between capsulotomy and formation of the macular hole.[2-4] The incidence of macular hole formation in fellow eyes has been reported as high as 22%. Certain identified risk factors, including macular cysts and visual acuity of 20/50 or less, increase the risk of hole formation in fellow eyes.[5]

Given the relatively low total of Nd:YAG laser energy applied (18 mJ in the right eye and 29 mJ in the left eye), it seems unlikely that the shock wave generated by the pulse directly caused the macular holes in our patient. This lack of an immediate direct effect is supported by an initial postoperative visual acuity of 20/20 in each eye.

We recommend a vitreous examination when considering an eye for Nd:YAG laser posterior capsulotomy. In patients with previous complications in an eye, particularly macular holes, and without a complete posterior separation in the fellow eye that may need an Nd:YAG capsulotomy, it would seem prudent to consider waiting for the spontaneous posterior separation to become complete. Even in cases where posterior capsulotomy is clinically indicated, ophthalmologists should consider vitrectomy to relieve all posterior retinal traction.

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Bilateral Diffuse Choroiditis and Exudative Retinal Detachments With Evidence of Lyme Disease

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Tick-borne *Borrelia* infections are worldwide in distribution. Ocular symptoms include hemorrhagic conjunctivitis, dendritiform keratitis, iritis, iridocyclitis, retinal vasculitis and hemorrhages, optic disk edema, and retrobulbar neuritis.[1-5]

A 32-year-old woman was admitted with a 14-day history of bilateral blurred vision, metamorphopsia, and ocular pain. These symptoms had been preceded by a "flu-like" illness. The referring ophthalmologist had made the diagnosis of Vogt-Koyanagi-Harada disease and had prescribed systemic oral corticosteroids (72 mg/day of prednylidene). At that time, visual acuity was 20/40 in both eyes. The patient observed further blurring, however, and was admitted with a visual acuity of R.E.: 20/100 and L.E.: 20/66. Prednylidene intake was at 36 mg/day. This dosage was continued throughout the clinical and laboratory examinations.

Results of slit-lamp examination disclosed bilateral inflammatory cells in the anterior chamber and vitreous. Exudative retinal detachments that extended peripherally between the 4 o'clock and 8 o'clock meridians were noted in both eyes (Fig. 1). Cystoid maculopathy in the central fundus regions was also observed. Results of Octopus and Goldmann perimetry showed paracentral scotomas. Corneal sensitivity was normal and no exophthalmos was present. Intraocular pressure was 12 mm Hg by applanation tonometry. Fluorescein angiography was repeated and disclosed choroidal lesions (Fig. 2). A thickening of the choroid was noted on B-scan ultrasonography.

Results of a complete physical examination ruled out both neoplasms and sarcoidosis. A slight hypacusis (familial by history) and signs of meningitis were found. Results of cerebrospinal fluid analysis showed a lymphocytic pleocytosis with 91 cells and a protein level of 52 mg/dl.

Differential blood cell count showed a slight leukocytosis of 11,900/mm^3 with a lymphocytosis of 54%. Serologic markers for sarcoidosis

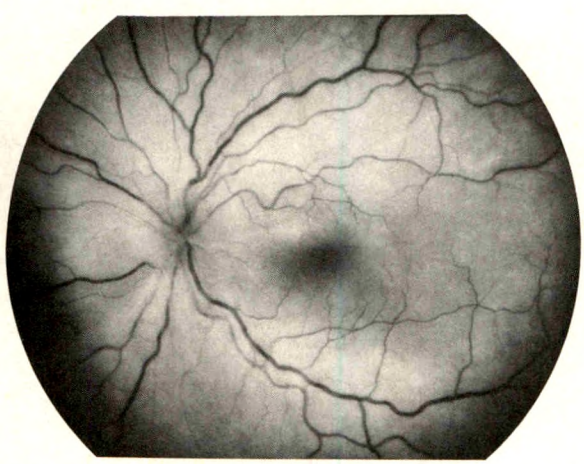


Fig. 1 (Bialasiewicz and associates). Diffuse choroidal infiltration with exudative retinal detachment, disk edema, and cystoid macular edema in the left eye. Visual acuity is 20/100.

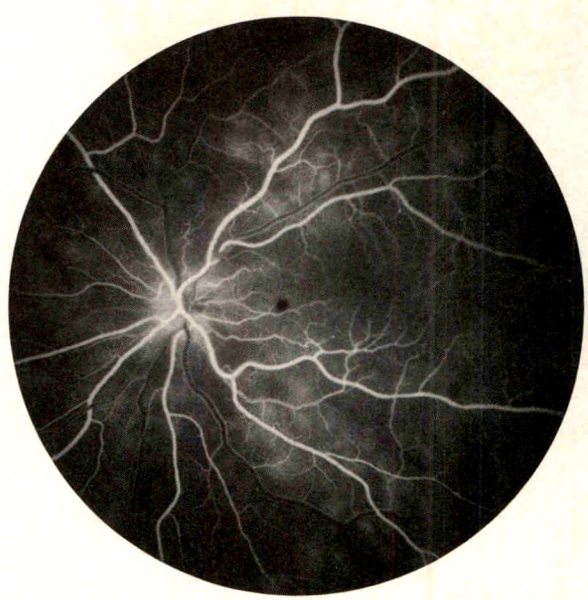


Fig. 2 (Bialasiewicz and associates). Hyperfluorescence at the optic disk in the left eye. Note the disseminated choroidal lesions with the mottled appearance of the retinal pigment epithelium.

were negative. This supported the clinical and x-ray findings. Results of hemoglobin electrophoresis were normal, and the HLA pattern was not suggestive for Vogt-Koyanagi-Harada disease. Results of serologic tests for human immunodeficiency virus, herpes simplex virus, rubella, coxsackie, (para)influenza, measles, Epstein-Barr virus, *Yersinia*, *Salmonella*, *Treponema pallidum*, and Q fever were unremarkable. Tumor markers carcinoembryonic antigen, CA 19-9, and CA 125 were also unremarkable. The results of a Lyme-immunofluorescent test were 1:640 (normal, <1:80), and a Lyme-IgM-immunofluorescent test, 1:40 (normal, <1:10); the results of a Lyme-immunofluorescent test in the cerebrospinal fluid were marginal.

When the results of the Lyme-immunofluorescent test were obtained, 100 mg of doxycycline twice daily was started orally for seven days. Meningeal symptoms resolved, and visual acuity was rapidly restored. Seven days after therapy, visual acuity was 20/25 in both eyes. Although a slight bilateral disk edema remained, the exudative retinal detachments had almost disappeared. Control titers at the end of therapy were as follows: Lyme-immunofluorescent test, 1:320; Lyme-IgM-immunofluorescent test, <1:20; and Lyme-immunofluorescent test in cerebrospinal fluid, <1:10. The number of cells in the cerebrospinal fluid was 15/dl.

This study indicates a strong correlation between choroidal lesions, optic disk edema, bilateral central exudative retinal detachments, and lymphocytic pleocytosis in the cerebrospinal fluid, and positive Lyme serologic findings. The clinical course of the disease (worsening of symptoms with corticosteroids, rapid resolutions with doxycycline) and the decreasing serum Lyme-IgM-immunofluorescent test (as well as the Lyme-IgG-immunofluorescent test) after successful therapy strongly suggest an infection with *Borrelia* species. In selected diffuse choroidal lesions, we propose that a thorough laboratory examination should be performed, including tests for Lyme disease.

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Venous Stasis Retinopathy and Gaisbock's Syndrome

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In many previous studies central retinal vein occlusion has been related to generalized vascular disease.[1] Venous occlusive disease in the eye has also been reported as a complication of hyperviscosity (primary and secondary polycythemia, myeloma, and acute dehydration), coagulation disorders, systemic vasculitis (systemic lupus erythematosus and scleroderma), and abnormalities of the optic disk (drusen and sarcoid). We recently studied a case of nonischemic central retinal vein occlusion associated with Gaisbock's syndrome.

A 56-year-old man in apparent good health reported a one-month history of decreased vision in the left eye. Best corrected visual acuity was R.E.: 20/20 and L.E.: 20/200+. There was sludging of blood in the conjunctival capillaries. A subtle left afferent pupillary defect was noted. Intraocular pressure was 18 mm Hg in both eyes. Slit-lamp biomicroscopy demonstrated a few vitreous cells in the left eye, and both disks were hyperemic and congested. In the right eye there was moderate retinal venous dilation and tortuosity, with scattered small inner retinal hemorrhages in all four quadrants. The macula was not edematous on clinical examination. Retinal venous congestion and hemorrhage in the left eye were more marked, with peripapillary cotton-wool spots and advanced cystoid macular edema. There

was no anterior or posterior segment neovascularization in either eye. Fluorescein angiography showed slightly prolonged arm to eye and arteriovenous transit with moderate late leakage from the disk, and a largely intact perifoveal capillary net in the left eye. In the right eye an inferonasal peripapillary hyperfluorescence was related to a small cotton-wool spot. Results of physical examination were unremarkable and blood pressure was normal. The patient was a 50 pack-year cigarette smoker.

Results of a detailed systemic evaluation, including studies of glucose tolerance, thyroid and renal function, serum protein and lipoprotein electrophoresis, antinuclear antibody, lupus erythematosus cell preparation, chest film, and SMA 18 were unremarkable. The patient's hemoglobin level was 18 g/100 ml and his hematocrit was 54%. The red cell mass was 20 ml/kg of body weight and the plasma volume was 24 ml/kg of body weight, both in the low normal range.

In order to maintain intraocular pressure in the low normal range, the patient was treated with aspirin once daily and timolol. During the ensuing year, visual acuity in the left eye became limited to 6/200 because of macular hemorrhage and edema. The right eye has retained a visual acuity of 20/20 with unchanged mild venous stasis, a few peripapillary retinal hemorrhages, and no macular edema.

In 1905, Gaisbock[2] described a syndrome that has been characterized recently by a decrease in plasma volume. Despite a decreased cell mass, there is a resulting relative increase in the hemoglobin level and hematocrit. Patients with Gaisbock's syndrome are often obese, and may have mild cardiovascular complications. The pathophysiology is unclear and may be multivariate. Both smoking and stress-induced inhibition of nocturnal antidiuretic hormone release, with resulting diuresis, have been implicated, but other than nondiuretic reduction of blood pressure in hypertensive patients, there is no specific approach to therapy.[3,4]

The mechanism for venous stasis and central venous thrombosis in this group of patients may be more complex than relative hyperviscosity on the basis of decreased plasma volume. Until a patient's hematocrit is over 60%, there is generally little measurable increase in blood viscosity. The viscosity in our patient was normal. It is not clear whether an unusual pathway in the genesis of accelerated vascular disease underlies the syndrome, or whether patients with Gaisbock's syndrome comprise an unusual subset of patients with atherosclerotic cardiovascular disease.

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Presumed Thrombotic Thrombocytopenic Purpura Associated With Bilateral Serous Retinal Detachments

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An 18-year-old woman reported a decrease in vision. On examination, bilateral, large, yellow subretinal infiltrates were noted (Figure, left) with overlying, bullous retinal detachments, a small subconjunctival hemorrhage, and ankle edema. The patient had no history of hematologic problems. Angiography showed hyperfluorescence corresponding to the subretinal infiltrates with marked late subretinal leakage (Figure, right). Visual acuity was R.E.: counting fingers and L.E.: 20/200. Her hematocrit fell to 13.8%, and her platelet count fell to 6,000/mm^3. Results of a blood smear showed schistocytes, and the bone marrow was hypercellular. Results of clotting studies showed a concentration of fibrin degradation products of >40 μg/ml (normal, <10 μg/ml). Pelvic ultrasound showed a 20-week size dead fetus. Uterine evacuation with prostaglandin



Figure (Hemeter). Left, Fundus on day of admission. Note yellow subretinal infiltrates and bullous retinal detachments. Right, Results of fluorescein angiogram on day of admission. Note early subretinal hyperfluorescence with marked late subretinal leakage.

induction was performed, and the patient reported improved vision soon afterward. Results of blood studies improved after three days of plasmapharesis. Results of ophthalmoscopic examination on follow-up were normal, and her visual acuity was 20/20 in both eyes. Her hematocrit was 29% and platelet count was 220,000/mm^3. Repeat angiography at this time showed only localized areas of background hypofluorescence with no subretinal leakage.

This patient's hematologic findings did not lend themselves to precise diagnosis. Two consulting hematologists concluded that she had a microangiopathic hemolytic anemia, which includes both thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome. Disseminated intravascular coagulopathy was suggested by both the presence of a dead fetus and increased fibrin degradation products. Although she had no neurologic symptoms, the patient's prompt improvement after plasmapharesis argues most strongly for thrombotic thrombocytopenic purpura.

In seven reported cases of serous retinal detachments in thrombotic thrombocytopenic purpura and disseminated intravascular coagulopathy, only two patients survived.[1-4] Both of these patients had thrombotic thrombocytopenic purpura, and both experienced loss of vision well after hospitalization.[4] Of the five patients who died, two reported a loss of vision shortly before their death, and two were found to have retinal detachments at autopsy. One patient, who experienced loss of vision caused by choroidal infiltrates, developed retinal detachments the day after admission.[3] This patient also had a history of anemia and thrombocytopenia.

This case shows that vision loss because of serous retinal detachments is not just a late manifestation of thrombotic thrombocytopenic purpura or disseminated intravascular coagulopathy, but can be the first symptom. Ophthalmologists should be aware of these symptoms in their differential diagnosis of serous retinal detachments with subretinal exudates even when there is no history or sign of a bleeding diathesis. An accurate and early diagnosis may be lifesaving.

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Propionibacterium acnes Lens Abscess After Traumatic Implantation of Intralenticular Cilia

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Propionibacterium acnes, an infrequent cause of postoperative or posttraumatic bacterial endophthalmitis,[1,2] has been linked to a unique postcataract extraction uveitis syndrome consisting of late-onset chronic indolent uveitis with recurrent hypopyon.[3-5] This may respond initially to corticosteroids and topical antibiotics, but recurs, ultimately leading to frank bacterial endophthalmitis that requires systemic and intravitreal antibiotics, vitrectomy, or removal of the intraocular lens.

A 26-year-old man was referred to our institution four hours after sustaining penetrating trauma to his left eye. An air-compressed staple gun had accidentally discharged, embedding a staple in the lateral aspect of his globe. A coworker removed the staple and discarded it. At our clinic, the patient complained of only moderate pain and a slight decrease in vision in the left eye.

The visual acuity was R.E.: 20/15 and L.E.: 20/30. Slit-lamp biomicroscopy of the left eye showed diffuse subconjunctival hemorrhage from the 3:00 to 8:30 o'clock positions and a penetrating wound at the 3:00 o'clock site, 5.0 mm posterior to the corneoscleral limbus. There was no uveal or vitreous prolapse. Two eyelashes were embedded in the crystalline lens and mild cataractous changes were noted. Ocular tensions were R.E.: 15 mm Hg and L.E.: 0 mm Hg.

Ophthalmoscopic examination disclosed an apparently old, horseshoe-shaped tear in the upper temporal quadrant with pigmentary reaction. No hemorrhage was present at this site; however, diffuse vitreous hemorrhage with layering inferiorly was noted. The retina was attached. The patient underwent emergency exploration of the globe and repair of the scleral perforation. Cryotherapy was applied to the horseshoe-shaped tear. Five days of broad-spectrum intravenous antibiotics (cefazolin sodium and gentamicin) were administered, along with topical antibiotics and corticosteroids. Intraocular inflammation resolved except for progression of the traumatic cataract.

Three weeks later, the patient again complained of decreased vision and pain in the traumatized eye. Mild anterior chamber inflammation was observed. Infiltrates were now present as sheaths around the two intralenticular cilia. The patient was admitted for treatment with topical and intravenous antibiotics (cefazolin sodium and gentamicin) and topical corticosteroids. Pain and intraocular inflammation quickly resolved. Three days later the patient was discharged on a treatment regimen of oral dicloxacillin, topical antibiotics, and topical corticosteroids.

Four days after discharge, the patient complained of severe pain and decreased vision. A progressive lenticular abscess was present surrounding the two cilia. Pars plana vitrectomy and lensectomy were performed, along with injection of intravitreal cefazolin sodium, gentamicin, and dexamethasone. Two cilia were removed from the lens abscess. Analysis of vitreous aspirate showed a few gram-positive cocci and moderate numbers of pleomorphic gram-positive rods. Anaerobic cultures of the vitreous and cilia disclosed *P. acnes*, sensitive to beta lactam antibiotics with intermediate susceptibility to aminoglycosides.

The postoperative course was unremarkable. Four weeks after surgery, the eye was quiet with a best corrected visual acuity of L.E.: 20/30.

The role of *P. acnes* in intraocular inflammation has been studied. Frank endophthalmitis has been reported after intraocular surgery and trauma.[1,2] A more unusual postoperative syndrome has been described by Meisler and coworkers[3,4] and by others[6] in patients who have undergone extracapsular cataract extraction and intraocular lens implantation. *Proprionibacterium acnes* seem to promote the development of a delayed-onset low-grade form of granulomatous uveitis. This may appear as a recurrent hypopyon initially responsive to topical corticosteroids. More obvious signs of endophthalmitis develop when corticosteroids and antibiotics are tapered. The presence of a foreign body (intraocular lens) and residual lens protein (after extracapsular cataract extraction) have been implicated as important co-

contributors to this form of inflammation, which has some of the clinical and cytologic characteristics of phacoanaphylactic endophthalmitis.[3-6] Known to have adjuvant qualities, *P. acnes* may enhance the development of a phacoantigenic inflammation.[5]

Our case indirectly supports the hypothesis of Meisler and coworkers in that the combination of a foreign body (in our case, two cilia), lens protein material, and *P. acnes* resulted in the gradual development of intraocular inflammation. The cilia probably carried the *P. acnes*, frequently part of their normal flora, into the crystalline lens. Over a period of a few weeks, pericilial intralenticular abscesses developed. The resulting inflammation responded initially to corticosteroids and antibiotics but recurred when these medications were tapered. Gradually, a more profound intralenticular abscess developed, leading to frank endophthalmitis that resolved only after lensectomy, vitrectomy, and removal of the cilia.

This case illustrates two fundamental aspects of *P. acnes* endophthalmitis. First, *P. acnes* may act as an adjuvant, enhancing intraocular inflammation when lenticular integrity has been compromised. Second, significant *P. acnes* outgrowth may occur only after an extended period of time. This organism is anaerobic, requiring low oxygen tensions such as those found within the crystalline lens and vitreous.

This case emphasizes the importance of considering *P. acnes* as a contributing factor in intraocular inflammation in posttraumatic and postoperative clinical settings.

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A Complication From Alcohol-Swabbed Tonometer Tips

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Concern for potential transmission of viruses by tonometer tips has prompted recommendations for effective sterilization techniques.[1] A recent study proposed routine disinfection of tonometer tips with 70% isopropyl alcohol wipes.[2] We report a complication from this technique.

A 38-year-old woman with type I diabetes mellitus complained of discomfort immediately after applanation tonometry of the right eye. One drop of fluorescein sodium had been instilled in each eye and the tonometer tip had been swabbed with a 70% isopropyl alcohol wipe immediately before intraocular pressure measurements were taken. No symptoms were noted in the left eye. Results of slit-lamp examination of the right eye disclosed a circular area of corneal epithelial opacification corresponding to the size of the tonometer tip (Fig. 1). This area stained faintly with fluorescein but stained strongly with rose bengal. The eye was patched for approximately two hours, and then the patch was removed. The patient was comfortable immediately after the removal of the patch. Approximately two to three hours later, however, she noted significant discomfort that lasted 16 hours. The discomfort resolved by the next day.

A similar but lesser degree of corneal opacification occurred in a second patient when to-

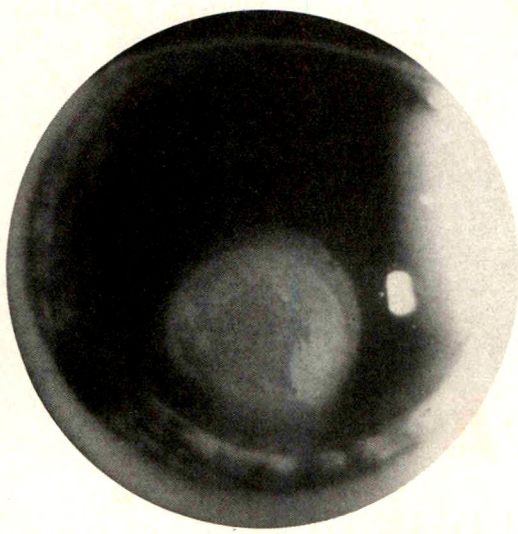


Fig. 1 (Soukiasian and associates). Two circular areas of corneal opacification after two applications of the tonometer tip. The tip had been swabbed with a 70% isopropyl alcohol wipe immediately before applanation.

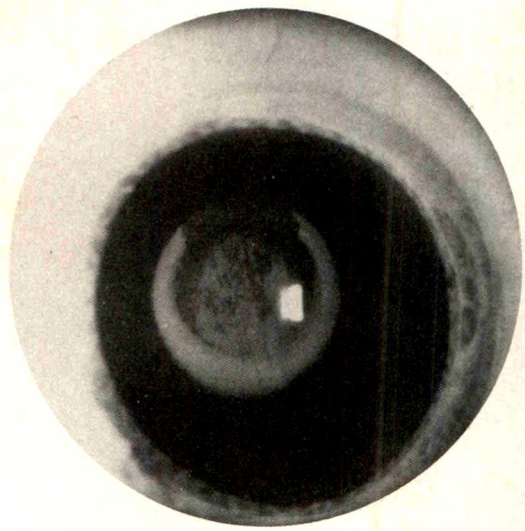


Fig. 2 (Soukiasian and associates). A less dense corneal opacification after applanation tonometry. The tip had been swabbed with a 70% isopropyl alcohol wipe 30 seconds before applanation.

nometry was performed 30 seconds after the tonometer tip was swabbed with 70% isopropyl alcohol. The opacity resolved in 24 hours (Fig. 2).

The recent isolation of the human immunodeficiency virus from the tears of patients with the acquired immunodeficiency syndrome[3] and the isolation of herpes simplex virus type 1, hepatitis B virus, and adenovirus have renewed concerns for potential iatrogenic transmission of these diseases by the ophthalmologist. Variability still exists, however, in the proper handling of tonometer tips by clinicians. Because a short and simple cleaning technique is desirable in the clinical setting, swabbing the tonometer tip with a 70% isopropyl alcohol wipe is a practical, convenient, and effective method for removing both herpes simplex virus type 1 and adenovirus from tonometer tips.[2,4] Further studies may prove this technique to be effective for the human immunodeficiency virus.

To avoid complications after disinfecting the tonometer tips, a minimum waiting period of one minute should be observed. Ideally, the tonometer tip should be swabbed immediately after each use. This should allow enough time for the tip to dry before using it with the next patient. If this procedure is not followed, however, the one-minute waiting period should be observed.

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Amiodarone Keratopathy in the Donor Cornea

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The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Army, the Department of Defense, or the U.S. Government.

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Verticillate keratopathy is a complication associated with systemic administration of amiodarone for control of refractory ventricular dysrhythmias.[1] When they occur, the symptoms are mild and include glare, mild blurring of vision, and halos around lights.[2] Most investigators have found that the keratopathy persists for several months after amiodarone has been discontinued. This prolonged effect can be attributed both to the long half-life of the drug (20 to 100 days) and to the slow turnover of the epithelial basal cells.[3] These cells contain lamellated lysosomal inclusions that are the clinicopathologic correlate of this disorder.[4]

A 52-year-old man was treated with a regimen of amiodarone 300 mg twice daily for refractory ventricular tachycardia. Six months after starting the amiodarone therapy, the patient noted a "rainbow-like" halo around lights. The patient died shortly thereafter from complications related to heart disease. His eyes were enucleated and examined by biomicroscopy after being stored for ten hours in a moist, sterile chamber. Typical 4+ verticillate keratopathy[5] was noted (Fig. 1). The corneoscleral button was removed and stored in refrigerated chondroitin sulfate medium for 14 hours before an 8.25-mm central button was removed for transplant.



Fig. 1 (Garrett, Waterhouse, and Parmley). Donor cornea shows typical amiodarone keratopathy ten hours after enucleation.

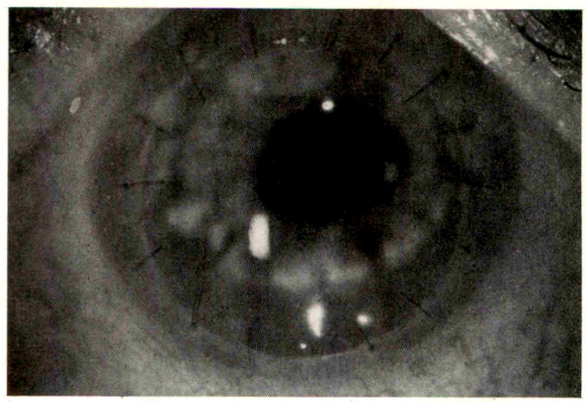


Fig. 2 (Garrett, Waterhouse, and Parmley). Two weeks after penetrating keratoplasty, the cornea shows resolution of keratopathy in the graft.

The transplant recipient was a 72-year-old woman with pseudophakic bullous keratopathy, lens-induced uveitis, and secondary glaucoma. An 8-mm trephine was used to remove the host corneal button and an intraocular lens exchange was performed. Without removing its epithelium, the donor corneal button was positioned, using 10-0 nylon interrupted sutures.

Amiodarone-induced epithelial whorls, visible in the grafted donor button for the first few days after surgery, disappeared after two weeks (Fig. 2). No adverse effects have been noted and the graft has remained clear.

The rapid regression of the keratopathy may be related to either a redistribution of the drug from the donor material into a drug-free tissue reservoir, or to a rapid repopulation of the donor cornea with recipient-derived epithelium. We believe that donor corneas with amiodarone keratopathy can be used safely in penetrating keratoplasty, and that it is not necessary to remove the affected epithelium.

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Anaerobic *Capnocytophaga* Corneal Ulcer

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A healthy 56-year-old woman complained of pain and decreased vision. She had a corneal ulcer just below the visual axis with approximately a 3-mm hypopyon. No organisms were found in scrapings from the ulcer and cultures were initially negative. Although a regimen of 15 mg/ml of gentamicin sulfate was started, there was no effect. After several days, the anaerobic cultures grew *Capnocytophaga*, which was resistant to both the aminoglycosides and sulfa compounds. The patient was then placed on intensive, topical, fortified cephalosporin, and she rapidly responded.

Capnocytophaga is characterized by its gliding mobility on solid surfaces. This organism was formerly called *Bacteroides ochraceus* and is identical to biogroup DF-1 of the Centers for Disease Control. It is a slender, fusiform, gram-negative bacillus that grows only in anaerobic, carbon dioxide-enriched atmospheres. This organism is oxidase-negative and catalase-negative and does not grow on MacConkey's agar. It may produce a yellow pigment on solid media and fermentatively metabolize sugar even in the presence of oxygen.

The principal habitat of this organism appears to be in the oral cavity and it may be responsible for periodontitis. It is usually not a pathogen unless the patient is immunocompromised.[1]

Roussel, Osato, and Wilhelmus[2] described two patients with ocular *Capnocytophaga* who were treated successfully with topical and subconjunctival clindamycin.[2] As there are no unique clinical features of *Capnocytophaga* keratitis, ophthalmologists should be aware of the need to use culture media that can detect both facultative and obligate anaerobes. Because this group is uniformly resistant to aminoglycosides, treatment with cephalosporins or clindamycin is recommended.

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Pupillary Testing Using the Direct Ophthalmoscope

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Clinicians usually perform the alternating light test for relative afferent pupillary defects by shining a hand-held light in each eye of a patient who is looking at a distant fixation target.[1] Although this technique works well with cooperative patients, some children tend to look at the light and thus their pupillary responses to near obscure their responses to light. In these cases a direct ophthalmoscope with a halogen bulb can be used to examine the pupils. The red reflex can be seen to illuminate the pupil by looking through the ophthalmoscope at a distance of 1 meter. The patient is asked to look at the light from the ophthalmoscope, and the light is shone alternately on each pupil. When the room is completely dark, the pupillary responses are usually easy to see against the background provided by the red reflex, and problems caused by near responses are minimized.

TABLE
RESULTS OF PUPIL TESTING
WITH THE OPHTHALMOSCOPE

RELATIVE AFFERENT PUPILLARY DEFECT DENSITY (LOG UNITS)	NO. OF PATIENTS	NO. WITH ABNORMAL RESULTS*
0.3	5	4
0.6	6	4
0.9	2	2
1.8	1	1

*Alternating light test using the red reflex.

In order to determine the sensitivity of this technique, I studied a consecutive series of 14 adults who had relative afferent pupillary defects. Three patients had anterior ischemic optic neuropathy, two had pituitary tumors, six had multiple sclerosis, one had optic neuritis, one had an idiopathic optic neuropathy, and one had central serous retinopathy. I measured the relative afferent pupillary defect using neutral density filters and a Finhoff transilluminator light,[2] and I tested the pupillary responses with the ophthalmoscope using alternation rates of one second and three seconds per eye. I judged the presence of an afferent pupillary defect by comparing the amplitude of the initial constriction of each pupil.[3]

I found that 11 of the 14 patients had relative afferent pupillary defects that were detectable using the ophthalmoscope (Table). The defect was easier to see using the three-second alternation rate in four patients, and using the one-second rate in one patient. In one other patient, the defect was easier to see with the ophthalmoscope than with routine testing. Of the three patients with no detectable relative afferent pupillary defect using the ophthalmoscope, one had small pupils that precluded observation of the red reflex, one had central serous retinopathy, and the third had only a 0.3-log unit defect.

The ophthalmoscope can also be used to observe pupillary responses while testing for the paradoxical constriction to darkness seen in some children with retinal disorders[4,5] and optic nerve hypoplasia (personal observation). While the room lights are turned on and off by an assistant, the pupils are observed from the side with the intensity of the ophthalmoscope light decreased so that the red reflex is just visible.

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Optic Nerve Swelling Secondary to the Obstructive Sleep Apnea Syndrome

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The obstructive sleep apnea syndrome is characterized by an interruption of normal breathing during sleep secondary to airway obstruction below the nasopharynx. The diagnosis is confirmed by polysomnography, which documents periods of apnea during sleep. We recently treated a patient with obstructive sleep apnea syndrome who developed secondary disk edema. The disk edema resolved after therapeutic tracheostomy.

A 46-year-old man reported an eight-month history of progressive fatigue, low-grade bifrontal headaches, daytime sleepiness, decreasing sexual function, and increasing episodes of visual obscurations. On additional questioning, the patient reported a 55-lb. weight gain over the previous year, a failing short-term memory, and a decreasing ability to calculate numbers. His wife had also noted loud snoring and choking sounds followed by

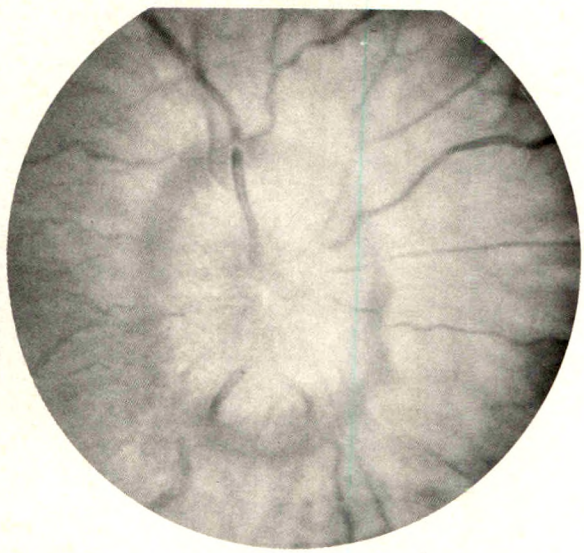


Fig. 1 (Bucci and Krohel). Right optic disk edema secondary to obstructive sleep apnea.

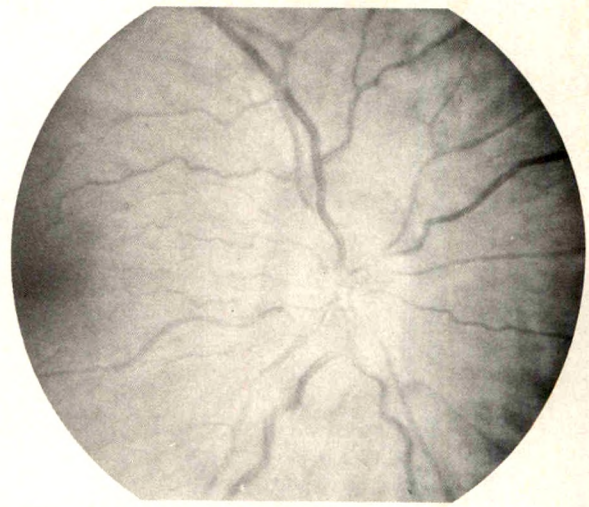


Fig. 2 (Bucci and Krohel). Improvement of the right optic disk edema after permanent therapeutic tracheostomy. Disk edema resolved completely after four months.

intermittent periods of silence. Results of physical examination showed generalized but not morbid obesity (6 ft., 235 lbs.), a short, thick neck, hypertrophic tonsils and adenoids, an elongated soft palate, asymmetric swollen optic disks, and mild ankle edema. Visual acuity was R.E.: 20/25 and L.E.: 20/20−3. An afferent pupillary defect was not observed. On ophthalmoscopy, bilateral swelling and hyperemia of the optic disks were noted, with the right disk greater than the left (Fig. 1).

Computed tomography showed mild swelling of the right optic nerve. The results of a lumbar puncture were within normal limits, with clear fluid, three normal lymphocytes, a protein level of 48 mg/100 ml, a glucose level of 78 mg/100 ml, and an initial pressure of 170 mm H_2O. Results of pulmonary function tests disclosed a minimal restrictive deficit. Polysomnography confirmed the diagnosis of obstructive sleep apnea by demonstrating 82 episodes of apnea (greater than ten seconds) over 4.6 hours of sleep.

One month later, the patient underwent rhinoplasty to correct a deviated septum and to enlarge the nasal passages. His disk edema remained unchanged. Two weeks later a uvulopalatopharyngoplasty was performed, with resection of the tonsils, uvula, nonmuscular soft palate, and redundant mucosa of the posterior pharynx. In conjunction with the uvulopalatopharyngoplasty, a temporary tracheostomy was performed to give the edematous postoperative pharyngeal tissues time to heal. The patient's systemic symptoms improved significantly after these procedures, but his condition rapidly deteriorated after the temporary tracheostomy was removed. The placement of a permanent tracheostomy led to the resolution of all of the patient's major complaints and to a marked improvement in his optic nerve swelling after six weeks (Fig. 2). Four months later, the optic nerve swelling was completely resolved in both eyes.

The obstructive sleep apnea syndrome is a potentially life-threatening condition. It is characterized by periodic interruption of air flow and arterial oxygen desaturation, in spite of sustained or increased respiratory effort. Increased respiratory effort against an obstructed upper airway stimulates cardiac arrhythmias, and patients with sleep apnea are at significantly increased risk for sudden cardiac death during sleep.[1]

The chief complaint of patients with this syndrome is usually excessive daytime sleepiness. The disease is observed most frequently in middle-aged obese men. Family members may report a long history of loud snoring interspersed with periods of silence. Patients are usually unaware that their sleep is being interrupted by apnea, although this may occur hundreds of times per night, making restful sleep impossible. Sleep deprivation can lead to per-

sonality and intellectual changes, including emotional outbursts, excessive irritability, deep depression, memory loss, headache, and the inability to concentrate.

Papilledema secondary to pulmonary insufficiency has been previously reported.[2,3] Hypercapnia, hypoxia, and increased venous pressure are the most frequently implicated factors. An increased intracranial pressure is also observed in most of these cases.

Obstructive sleep apnea is characterized by hypercapnia and hypoxia only during sleep. Blood gases during waking hours are usually normal. Episodic increases in intracranial pressure have been reported in patients with sleep apnea.[4] This may have been responsible for the optic disk swelling in our patient.

Ophthalmologists share the responsibility for recognizing and appropriately referring patients with this potentially fatal disease. This is especially important because long-term successful management of obstructive sleep apnea has been achieved with a nonsurgical, nonpharmacologic outpatient treatment. A new portable home device allows continuous positive airway pressure to be applied through a nasal mask at night. In therapeutic trials, this mode of treatment has been effective in treating patients with severe obstructive sleep apnea who previously required permanent tracheostomies.[5]

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Preoperative Evaluation of Lower Eyelid Blepharoplasty

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Realistic expectations on the part of both patient and surgeon are an important aspect of cosmetic surgery. Patients who desire lower blepharoplasty may be bothered by skin wrinkles, skin discoloration, shadows, and tissue bulges (Fig. 1). It is chiefly the bulging fat pouches and associated shadows that can be improved by lower blepharoplasty. The surgeon can produce a good approximation of this improvement by having the patient supine or by tipping the examining chair back. The orbital fat then falls posteriorly in the orbit because of gravity. The lower eyelid bagginess and the accompanying shadows will often be reduced substantially in the supine position (Fig. 2). In many instances the surgeon can gain a reasona-



Fig. 1 (Boynton). Preoperative appearance of lower eyelid fat bulges.



Fig. 2 (Boynton). Improved appearance with patient in supine position.

bly accurate idea of the cosmetic improvement to be expected after lower blepharoplasty and can share this with the patient using a mirror. A patient with realistic expectations is less likely to be disappointed with cosmetic surgery.

Eyelid Phimosis and Chronic Radiation Dermatitis Associated With Iridium Brachytherapy

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Radioactive plaque application with isotopes of cobalt, iodine, ruthenium, or iridium has become a popular treatment modality for posterior uveal melanomas. Late complications associated with this treatment have been described in approximately 40% of the patients. These complications include retinopathy, tumor vasculopathy, papillopathy, vitreous hemorrhage, cataract, punctal occlusion with epiphora, keratoconjunctivitis sicca, anterior uveitis, scleral necrosis, and diplopia.[1-3]

A 37-year-old woman had a six-month history of photopsia in her right eye. She was undergoing systemic chemotherapy for a previous infiltrating ductal carcinoma of the breast with positive axillary nodes. Examination disclosed a large, pigmented, nasal ciliochoroidal mass extending from the 2:30 to the 5 o'clock meridian. The mass involved the ciliary body and extended posteriorly to within 2 mm of the disk margin. Clinical estimate of size was 16 × 15 × 10 mm. An inferior nonrhegmatogenous retinal detachment and a shallowly detached macula were noted. Standardized echography confirmed a choroidal mass with low-medium internal reflectivity and a maximum thickness of 10 mm. The mass was believed to be consistent with a primary ciliochoroidal melanoma; however, because of the patient's previous carcinoma of the breast, a fine needle aspiration biopsy was performed to differentiate between a primary and metastatic intraocular tumor. Cytologic findings were consistent with malignant melanoma, and after an explanation of the various therapeutic modalities, the patient elected to undergo treatment with radioactive plaque application.

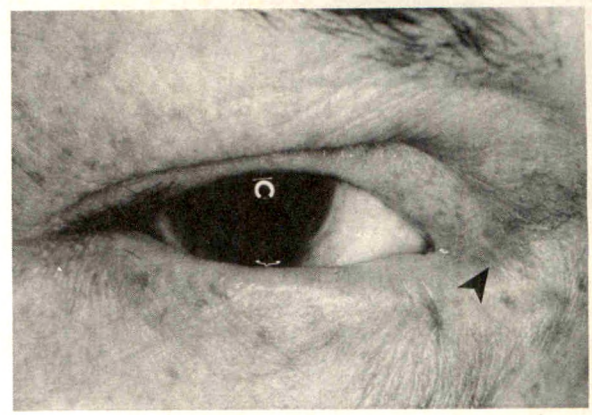


Figure (Kronish, Mieler, and Dortzbach). Upper and lower eyelid induration, extensive loss of eyelashes, scarring and occlusion of the superior and inferior puncta, and phimosis of the medial commissure after iridium brachytherapy. Arrowhead indicates the pretreatment location of the medial canthal angle.

Because of the relatively large tumor size, iridium-192, a high-energy gamma ray emitter, was chosen as the radioactive isotope for treatment. A plaque with a total activity of 64 mCi was applied to the medial aspect of the globe, corresponding to the position of the melanoma. Placement of the plaque was confirmed by transscleral transillumination techniques. The plaque was removed 49 hours later, by which time the radiation dose delivered to the tumor apex was 85 Gy, with the base receiving 296 Gy.

Three days later, the medial half of the right upper and lower eyelids became markedly indurated, with breakdown of the superficial skin. Oral and topical antibiotics were administered to treat the dermatitis. The swelling and redness of the eyelids persisted, however, and two months later, the patient noted the onset of excessive tearing and unremitting pain of the right eyebrow, eyelids, and eye. Narcotic analgesics were necessary to relieve the discomfort. Because of the chronic pain and cosmetic disfigurement, the patient began to withdraw socially.

Eight months after the plaque application, examination disclosed a visual acuity of 20/300

in the right eye, moderate swelling and erythema of the medial two thirds of the right upper and lower eyelids, extensive loss of eyelashes, scarring and occlusion of the superior and inferior puncta, and phimosis of the medial commissure (Figure). Nasally, the conjunctiva was scarred and contracted, the sclera was mildly thinned, and the cornea was superficially vascularized with focal epithelial defects. Moderate cellular reaction was noted in the anterior chamber, and iris stromal atrophy was observed nasally. Progressive regression of the inferonasal ciliochoroidal tumor down to a thickness of 3.5 mm was confirmed echographically, and there was complete resolution of the nonrhegmatogenous retinal detachment. Visual acuity in the left eye was 20/20, and the left eye and eyelids were normal.

Pain was partially relieved with frequent application of topical lubricants and cycloplegics for the keratopathy and anterior chamber reaction, and the eyelid inflammation became less severe over the next several months. Surgical management of the phimotic eyelids and occluded puncta was deferred pending further regression of the inflammatory changes. Cosmesis has been improved through the use of tinted spectacles, and by eye makeup to cover the residual dermatitis.

This patient developed chronic radiation dermatitis of the eyelids and phimosis of the medial commissure after iridium brachytherapy for choroidal melanoma. Also present were scleral thinning, anterior uveitis, chronic keratitis with corneal vascularization, loss of eyelashes, punctal occlusion, and epiphora. The role of the patient's chemotherapy in potentially altering or exacerbating the effects of radiation on the the periocular tissues is not fully known. Despite the preservation of partial vision and evident regression of the tumor, the chronic pain and cosmetic disfigurement resulting from this treatment have caused significant psychosocial effects in our patient. Radiation damage to the eyelids should be considered a potential complication of iridium brachytherapy, particularly in patients who have an anterior choroidal melanoma that involves the ciliary body.

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Correspondence

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Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Anterior Hyaloidal Fibrovascular Proliferation After Diabetic Vitrectomy

EDITOR:

In the article "Anterior hyaloidal fibrovascular proliferation after diabetic vitrectomy," by H. Lewis, G. W. Abrams, and G. A. Williams (Am. J. Ophthalmol. 104:607, December 1987), the authors described postoperative complications after diabetic vitrectomy, including recurrent vitreous hemorrhage, blood vessels or fibrovascular tissue on the posterior lens capsule, anterior extraretinal vascularization, traction detachment of the peripheral retina or ciliary body, and hypotony. These symptoms are similar to the syndrome of retrolenticular neovascularization described by Charles.[1]

Our patients with anterior hyaloidal fibrovascular proliferation frequently have a vitreous hemorrhage one or two days after pupillary dilation. These hemorrhages, observed on routine postoperative examination, are not associated with any clinical problems. The hemorrhages can occur weeks or months after surgery, and may be caused by tearing of the fine retrolenticular neovascular blood vessels by the movement of the pupil.

We classify our patients with anterior hyaloidal fibrovascular proliferation into two

groups. The first group develops a vitreous hemorrhage of presumed anterior origin after an otherwise uneventful and successful phakic diabetic vitrectomy. Retinal detachment is not a necessary part of the syndrome, as three of the authors' eight patients had vitreous hemorrhage only. The second group of patients develop anterior proliferative vitreoretinopathy, with the anterior loop traction producing hypotony, cataract, and peripheral traction detachment. This form of anterior hyaloidal fibrovascular proliferation is produced by extraretinal neovascularization.[2] We have observed similar cases in which massive sclerotomy fibrovascular ingrowth was the only finding at surgery. Our question for the authors, therefore, is whether the two cases with histopathologic documentation of extraretinal neovascularization reflect fairly the origin of their eight clinically described examples. Despite the authors' belief that a sclerotomy can be distinguished clinically from extraretinal sources of neovascularization, we believe that such a separation is difficult, if not impossible, and perhaps unimportant with regard to treatment.

In its milder form, anterior hyaloidal fibrovascular proliferation usually appears as a postoperative vitreous hemorrhage without iris neovascularization. When only mild vitreous hemorrhage is noted, then additive laser treatment is the obvious choice. In more severe cases, regardless of the source of the neovascularization, extensive surgery, including lensectomy and laser, is necessary to salvage the eye. Although removing the lens may seem paradoxical in a patient with diabetes, it is necessary in order to dissect the vitreous base. This is similar to removing the lens in severe cases of proliferative vitreoretinopathy. As the authors clearly indicate, the key point is to include lensectomy with vitreous base dissection.

Theoretically, extensive endolaser photocoagulation should decrease anterior hyaloidal fibrovascular proliferation. The new indirect laser scopes and the Spitznas-type operating microscope may allow for more intraoperative panretinal photocoagulation than can be done currently through the conventional operating microscope. Despite the widespread use of endolaser photocoagulation, the incidence of anterior hyaloidal fibrovascular proliferation continues to increase. The possibility that heavy laser photocoagulation compromises anterior choroidal and ciliary body circulation, thereby contributing to the syndrome, bears consideration.

We believe that in some instances, anterior hyaloidal fibrovascular proliferation may be present preoperatively. In some patients developing this syndrome we have observed adherent perilenticular hemorrhage before surgery, with blood cells trapped in the cleft between the posterior lens capsule and the detached anterior hyaloid face. If the patients who are at high risk for anterior hyaloidal fibrovascular proliferation could be identified reliably, then the initial vitrectomy, including lensectomy and vitreous base dissection, might offer the best prevention of this important complication of phakic diabetic vitrectomy surgery.

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Reply

EDITOR:

We thank Drs. Campo and Sipperley for their comments. Their observation of vitreous hemorrhage after pupillary dilation is interesting. We are uncertain about the mechanism involved, however, because in our experience, the anterior extraretinal vessels extend along the anterior hyaloid to the posterior lens surface and are not in contact with the iris.[1] Perhaps it is cycloplegia, rather than movement of the iris, that tears the neovascular vessels.

We believe that the eight clinical cases reported in our article describe the same entity as in the two cases of anterior hyaloidal fibrovascular proliferation with histopathologic evidence.[1] In the three eyes we treated with vitreoretinal surgery, we observed intraoperatively the anterior extraretinal fibrovascular tissue extending along the anterior vitreous to the posterior lens surface. We noted that the

sclerotomy wounds were well healed, and without proliferation of fibrous or vascular tissue beyond the healed wound. The remaining five eyes had anterior extraretinal vascular or fibrovascular tissue in multiple meridians that was not associated with the sclerotomy sites as seen by indirect ophthalmoscopy and scleral depression. Nonetheless, the clinical differentiation between extensive fibrovascular ingrowth and advanced forms of anterior hyaloidal fibrovascular proliferation may be difficult.[1] Although there are similarities between the cases of fibrovascular ingrowth[2,3] and our cases of anterior hyaloidal fibrovascular proliferation, we do not share the opinion of Drs. Campo and Sipperley that distinguishing between the two entities may be unimportant. We have found that early identification of anterior hyaloidal fibrovascular proliferation is critical so that laser treatment can be done at an early stage. We are not aware of any evidence that laser treatment is beneficial for fibrovascular ingrowth.

Rather than stratifying our patients into groups, we prefer to consider anterior hyaloidal fibrovascular proliferation as a continuum ranging from mild neovascularization, which usually appears with vitreous hemorrhage, to extensive fibrovascular proliferation with peripheral retinal detachment, cataract, and hypotony. We disagree that the more severe cases represent a form of anterior proliferative vitreoretinopathy. In our experience, anterior proliferative vitreoretinopathy does not have the vascularization that we believe characterizes anterior hyaloidal fibrovascular proliferation both clinically and histologically.[4]

We doubt that the incidence of anterior hyaloidal fibrovascular proliferation is increasing. Rather, since the initial observation of Charles, a greater understanding of anterior hyaloidal fibrovascular proliferation has resulted in better recognition. We also do not believe that laser endophotocoagulation is a causative factor in the development of this condition. During vitrectomy, phakic eyes rarely receive extensive anterior photocoagulation because of the risk of lens damage by the laser probe. We do, however, agree that compromise of the anterior choroidal and ciliary body circulation may play an etiologic role. Perhaps scleral buckling contributes to this vascular compromise.

We hope that the communication of Drs. Campo and Sipperley will stimulate others to assess critically this difficult postoperative complication.

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A Randomized Study of 5-Fluorouracil and Filtration Surgery

EDITOR:

In the article "A randomized study of 5-fluorouracil and filtration surgery," by J. M. Ruderman, D. B. Welch, M. F. Smith, and D. E. Shoch (Am. J. Ophthalmol. 104:218, September 1987), the authors compared the use of small subconjunctival doses of 5-fluorouracil to no antimetabolite therapy in 26 patients with a poor prognosis for filtration surgery. They concluded that in the group receiving active treatment, postoperative intraocular pressure was reduced significantly over six to 18 months.

Much larger study populations and longer follow-up periods are usually required to assess the overall safety of a new therapy. Low-incidence complications can only be detected in large-scale clinical trials. The authors' observation that corneal epithelial defects occurred in seven of the patients treated with

5-fluorouracil (50%) compared to only two of 12 patients (16.7%) in the control group (P = .11, two-sided) raises some concern regarding the safety of the therapy.

The National Eye Institute is sponsoring the Fluorouracil Filtering Surgery Study, which is a controlled clinical trial of 5-fluorouracil. Approximately 180 patients have been enrolled to date for long-term observation. Recommendations regarding the widespread use of any treatment ought to be based on careful weighing of the evidence for potential positive and negative effects. Thus, it seems prudent to await the results of this ongoing trial until 5-fluorouracil is adopted or rejected as standard therapy after filtering surgery in patients with a poor prognosis.

CURT D. FURBERG, M.D.
Winston-Salem, North Carolina

Reply

EDITOR:

To the best of our knowledge our study on the use of 5-fluorouracil after filtration surgery is the only one of the published studies to date that included a control group. We decided to publish the results because they supported results in the other studies, and because they provided some valuable insights into the effects of using a lower dosage of the medication.

The small number of patients in the study does make it difficult to detect increases in low-incidence complications (such as suprachoroidal hemorrhage or corneal ulceration). What is clear from our data is that even a lower dose of 5-fluorouracil causes a high incidence of common complications such as corneal epithelial defects. Our study also suggests that a lower dose of 5-fluorouracil will give approximately the same success rate as a higher dose, and that delaying injections until the presence of a watertight wound is established will decrease the number of wound leaks.

We commend Dr. Furberg and the others participating in the National Eye Institute study, and eagerly await the results. In the meantime, 5-fluorouracil, although not standard therapy, remains an option to the ophthalmologist performing filtering surgery in an eye with a poor prognosis for surgical success.

JON M. RUDERMAN, M.D.
DAVID WELCH, M.D.
DAVID SHOCH, M.D.
MARY FRAN SMITH, M.D.
Chicago, Illinois

The Effect of Twice Daily Nadolol on Intraocular Pressure

EDITOR:

In the article "The effect of twice daily nadolol on intraocular pressure" by G. R. Duff (Am. J. Ophthalmol. 104:343, October 1987), the author describes the ocular hypotensive efficacy of twice daily oral nadolol over a two-week period in a placebo-controlled long-term dosing study.

The efficacy of topical nadolol and its prodrug, diacetyl-nadolol, in lowering intraocular pressure has been previously reported.[1,2] The use of topical nadolol has been somewhat limited by the relatively short duration of its action, its association with blepharoconjunctivitis, and tolerance to its efficacy with long-term treatment. Oral nadolol, as reported by Williamson and colleagues,[3] appeared effective in patients with increased intraocular pressure.

In his article, the author found that the difference in ocular hypotensive efficacy between a placebo pill and 10 or 20 mg of oral nadolol twice daily was only 2 mm Hg. Williamson and associates found that 20 mg of oral nadolol daily had an ocular hypotensive efficacy of approximately 4 mm Hg, relative to the baseline. In that study, 40 and 80 mg of nadolol had an ocular hypotensive efficacy of 6 to 7 mm Hg, similar to that observed in the same study with topical 0.25% timolol.[3]

Duff, Watt, and Graham[4] recently reported that 20 mg of oral nadolol daily was similarly effective to topical 0.25% timolol twice daily. Both reduced intraocular pressure by approximately 5 to 6 mm Hg.[4] Some of their patients also underwent treadmill-exercise testing. The systemic beta-blockade found in these patients was greater with oral nadolol than with topical timolol.

Although the design and statistical methodologies differ somewhat among the various reports, I wonder if the author might comment on the differences in results.

GARY D. NOVACK, PH.D.
Irvine, California

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3. Williamson, J., Young, J. D. H., Atta, H., Muir, G., and Kadom, H.: Comparative efficacy of orally and topically administered beta-blockers for chronic simple glaucoma. Br. J. Ophthalmol. 69:41, 1985.
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Reply

EDITOR:

Dr. Novak correctly highlights the importance of taking study design into consideration when commenting on the results of clinical trials.

One of the prime objectives of the study by Duff, Watt, and Graham[1] was to study the systemic effects of nadolol and timolol. The various measurements were therefore made at peak effect, usually within two to six hours (and always within ten hours) of administration of the drug. In that study, 20 mg of nadolol were administered once daily.

Rennie and Smerdon[2] did not obtain a significant reduction in intraocular pressure 24 hours after the administration of 20 mg of nadolol on a once daily regimen. The study described in THE JOURNAL by one of us (G.R.D.) was designed to determine whether or not there was a significant reduction of intraocular pressure over the full 12-hour period on a twice-daily regimen. Measurements were made 12 hours after the administration of 10 or 20 mg of nadolol twice daily.

At peak effect, 20 mg of nadolol once daily produced a mean intraocular pressure of 17.7 mm Hg (mean intraocular pressure without treatment for this group was 22.5 mm Hg).[1] At minimum effect, 20 mg of nadolol twice daily resulted in a mean intraocular pressure of 19.7 mm Hg. The mean intraocular pressure of these subjects before treatment was 23.8 mm Hg.[2]

The results of these studies are consistent, and are not incompatible with those obtained by Williamson and associates.[3]

G. R. DUFF, F.R.C.S.Ed.
P. A. GRAHAM, F.R.C.S.
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A Double-Masked Study of Timolol and Pilocarpine Combined

EDITOR:

In the article "A double-masked study of timolol and pilocarpine combined" by P. J. Airaksinen, R. Valkonen, T. Stenborg, K. Takki, A. Klemetti, M. Kontkanen, and P. Oskala (Am. J. Ophthalmol. 104:587, December 1987), the authors suggest that a combination of 2% pilocarpine and 0.5% timolol is basically equivalent to 4% pilocarpine and 0.5% timolol. This conclusion is meaningless unless race and pigmentation of the iris are included in the study. Because the study was done in Finland, I assume that most patients had blue eyes. If that assumption is true, the study is not applicable to patients with dark brown irides. If the assumption is incorrect, then the study is in conflict with practically every other study done on the efficacy of pilocarpine in patients with darkly pigmented irides.

J. TERRENCE COYLE, M.D.
Bellevue, Washington

Reply

EDITOR:

Dr. Coyle is right in assuming that most of our patients had blue eyes. Of the 75 patients included in our study, six (8%) had dark irides and 69 (92%) had light irides. This distribution seemed so skewed that a comparison of drug efficacies between the two groups was not meaningful.

P. JUHANI AIRAKSINEN, M.D.
RISTO VALKONEN, M.D.
TAPIO STENBORG, M.D.
Oulu, Finland
KIRSTI TAKKI, M.D.
Lohja, Finland
ANNELI KLEMETTI, M.D.
Jyväskylä, Finland
MATTI KONTKANEN, M.D.
PERTTI OSKALA, M.D.
Savonlinna, Finland

Pyogenic Granuloma on a Dermis Fat Graft in Acquired Anophthalmic Orbits

EDITOR:

The article "Pyogenic granuloma on a dermis fat graft in acquired anophthalmic orbits," by A. D. Liszauer, S. Brownstein, and F. Codère (Am. J. Ophthalmol. 104:641, December 1987) was interesting. Pyogenic granulomas occurring in the socket after implantation of autogenous dermis fat grafts have been well described clinically,[1-7] but not with such an erudite discussion of their histopathology.

I would like to suggest two additional clinical environments that may have predisposed the sockets to forming pyogenic granulomas. The authors' photograph of Case 1 shows a diffusely inflamed socket with inflammation of the inferior fornix and a multilobulated pyogenic granuloma covering the entire surface of the graft. While small granulomas at the graft periphery are not uncommon (Fig. 1), the extensive socket inflammation demonstrated in this case is unusual. It is probably not, however, the result of a gaped region of the sutured margin as described by the authors. Delayed conjunctival migration over the graft, or central umbilication and necrosis of the graft (Fig. 2), often results in prominent granuloma formation over the graft surface. An ill-fitting prosthesis may also irritate both the inferior fornix and the anterior surface of the graft, causing abrasion of the graft's anterior surface with secondary granuloma formation.

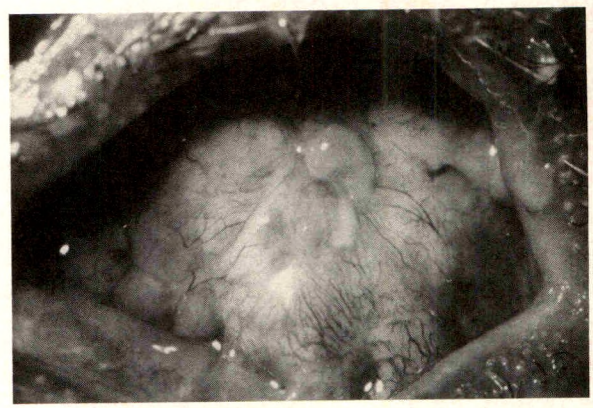


Fig. 1 (Bosniak). A small pyogenic granuloma at the suture line (host-donor conjunctival-dermal interface).

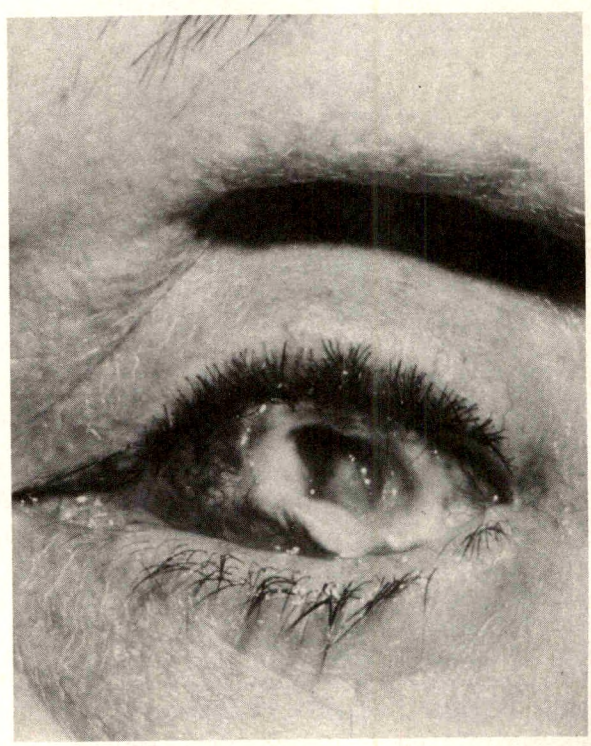


Fig. 2 (Bosniak). A rare case of marked postoperative central sloughing of dermis fat graft in a patient with collagen vascular disease.

Although autogenous dermis fat orbital implantation is a useful technique of socket reconstruction and is successful in the majority of properly selected cases, the procedure is not without complications. Great care and meticulousness must be exercised during each step of the procedure.

STEPHEN L. BOSNIAK, M.D.
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Reply

EDITOR:

Although orbital inflammation and an ill-fitting prosthesis certainly can play a role in the development of pyogenic granuloma, we do not believe they were important in the pathogenesis of our patient's lesion. Although the lesion was large, it was pedunculated and the stalk was only 2 to 3 mm wide. The epithelialization of the graft had proceeded normally after the implantation and the pyogenic granuloma originated from the lower suture line. The lesion had been present for at least one month during which time the patient was relatively asymptomatic. The moderate inflammation seen before surgical removal of the lesion seemed mostly to have followed the occurrence of the pyogenic granuloma, as we mentioned in our article. Thus, the inflammation seemed to be secondary to the pyogenic granuloma, rather than having been the cause of it, as Dr. Bosniak suggests in his letter. A custom-fit prosthesis, made from a molding of the orbital cavity, had been worn by the patient without any noticeable erosion of the conjunctiva, the inferior fornix, or the dermis fat graft.

We believe that the pyogenic granuloma developed into a large lesion because it grew over an extended period of time during which there was mechanical stimulation by the overlying prosthesis. This condition resolved after the lesion was removed, and did not recur in the follow-up period of eight months. During this time, the patient wore the same prosthesis. We agree with Dr. Bosniak that careful technique at the time of surgery and proper fitting of the orbital prosthesis are important for the prevention of complications in dermis fat orbital implantation. We believe that the occurrence of a postoperative pyogenic granuloma, especially in secondary implantation, is a benign and not uncommon complication without severe implications for the long-term prognosis of the graft.

ALLAN D. LISZAUER, M.D.
SEYMOUR BROWNSTEIN, M.D.
FRANÇOIS CODÈRE, M.D.
Montreal, Quebec, Canada

Incidence of Granulomatous Lesions in Postmortem Conjunctival Biopsy Specimens

EDITOR:

In the article "Incidence of granulomatous lesions in postmortem conjunctival biopsy specimens," by J. B. Saer, G. L. Karcioglu, and Z. A. Karcioglu (Am. J. Ophthalmol. 104:605, December 1987), the authors obtained biopsy specimens from the lower fornix of the conjunctival sac and diagnosed pinguecula in three of 58 specimens (5.2%). Pinguecula is an elastotic, degenerative, hyperplastic connective tissue situated in the bulbar conjunctiva on either side of the cornea in the interpalpebral area.[1] It appears that the conjunctival biopsy specimens obtained by the authors were located in an area away from the lower fornix. Similar indiscriminate

biopsy specimens from different sites in the conjunctival sac might be the reason for the wide range of positive results (14% to 71%) reported previously in patients with sarcoidosis.[2-4]

Because conjunctival biopsy is a blind procedure in the diagnosis of sarcoidosis, positive results support the diagnosis, but negative results do not rule out this disease. Still, if one chooses to do the conjunctival biopsy, then the biopsy specimen should be obtained from the lower fornix of the conjunctival sac so that it includes little bulbar tissue.

GURINDER SINGH, M.D.
Los Angeles, California

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Reply

EDITOR:

Dr. Singh's comment regarding the incidence of pinguecula in our specimens is well taken. We believe that the confusion has originated because we used the term "pinguecula" instead of "elastodysplasia" in our report. Pinguecula is best described as an elastodysplasia originating from excessive production of elastin material secondary to malfunctioning fibroblasts caused by radiation or other factors.[1] The focal degenerative changes observed in the subepithelial tissues of our biopsy specimens should have been described as areas of elastodysplasia instead of pinguecula. Although the classic picture of pinguecula, which includes elastotic degeneration and hyperplasia of the overlying epithelium with neovascularization, is seen only in the interpalpebral area, focal areas of elastodysplasia in subepithelial tissues can be detected anywhere in the conjunctiva, secondary to injured fibroblasts.

We would like to emphasize that the confusion has originated because of ambiguous terminology, and not because the biopsy specimens were obtained away from the lower fornix. All of our samples were obtained from the conjunctival tissue of the lower fornix as we have described previously.[2] We certainly agree with Dr. Singh that a blind conjunctival biopsy specimen should be obtained from the fornix without including any bulbar conjunctival tissue.

JOHN B. SAER, M.D.
GULER L. KARCIOGLU, M.D.
ZEYNEL A. KARCIOGLU, M.D.
New Orleans, Louisiana

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BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Uveitis. Pathophysiology and Therapy, ed. 2. Edited by Ellen Kraus-Mackiw and G. Richard O'Connor. New York, Thieme Medical Publishers, Inc., 1986. 257 pages, index, illustrated. $49.95

Reviewed by Robert C. Sergott
Philadelphia, Pennsylvania

Edited by Ellen Kraus-Mackiw and G. Richard O'Connor, this text is designed to describe recent clinical and experimental observations concerning intraocular inflammatory disease and to correlate these advances into practical applications. Consisting of seven chapters, each written by internationally recognized authorities, this volume accurately and clearly updates one of the most complex topics in ophthalmology.

Although a thorough introductory chapter outlines the fundamentals of immunology, the reader should have some familiarity with basic immunobiology to appreciate completely the sophisticated clinical and experimental data presented in the other six chapters. This book will help residents and practicing ophthalmologists who are committed to the care of patients with complex uveitis syndromes. The true merit of the book is the complete, comprehensive, and scientifically unbiased discussion of the always difficult and sometimes contradictory observations about uveitis. Each chapter is well illustrated with pathologic specimens, diagrams, and tables. The reference list in each chapter is superb, providing an invaluable compendium of primary sources.

The reader should not expect to find any magic cures for uveitis in this book. Rather, one of its highlights is Chapter 6, by William Dinning of Moorfield's Eye Hospital, which presents a succinct appraisal of various therapeutic strategies. Mr. Dinning stresses the importance of avoiding the use of potentially fatal cytotoxic agents except in the most desperate circumstances. Such caution cannot be overemphasized, especially when only theoretical and anecdotal data suggest their use.

The authors also discuss the newly described entities of the acute retinal necrosis syndrome, uveitis associated with acquired immunodeficiency syndrome (AIDS), and uveitis after intraocular lens implantation. Other syndromes such as toxoplasmosis and sympathetic ophthalmia, that have been recognized clinically for years, are updated with the most recent investigations concerning their immunopathogenesis.

This volume accomplishes its objective to report the most recent advances in uveitis and to place these facts into clinical perspective. This is a scholarly, scientific treatise to be read and re-read by students, researchers, and practitioners dedicated to clinical and experimental uveitis.

Vitreous Microsurgery, ed. 2. By Steve Charles. Baltimore, Williams and Wilkins, 1987. 235 pages, index, illustrated. $60.50

Reviewed by Thomas K. Krummenacher
St. Louis, Missouri

This book offers a logical, stepwise decision-making system for the management of vitreous pathology. The second edition, appearing six years after the original, was made necessary by

many recent advances in instrumentation. A strategy is proposed for dealing with most of the major challenges in vitreous surgery. There are also useful chapters on preoperative evaluation as well as the management of complications. These concepts are reinforced with diagrams, tables, and surgical algorithms. Although sometimes dogmatic, this concise, commonsense approach is effective. Interesting controversies covered include the author's preference for external drainage of subretinal fluid over internal drainage through a retinotomy. There is the expected debate concerning the value of delamination over perpendicular dissection of epiretinal membranes. Although this text is not intended to provide a broad view of the subject, these opinions are supported by the author's vast experience and are undeniably thought provoking.

Of particular merit is the chapter dealing with the general technique of posterior segment surgery. Here the author clarifies the objectives of modern vitreous surgery and offers many basic, but valuable, hints that have been omitted in other texts. A chapter on the use and complications of silicone oil would have been appreciated. Although not an in-depth review, the book is a worthwhile manual. It should be required reading for the beginner and is guaranteed to stimulate the most experienced.

Eyelid Tumors. Clinical Diagnosis and Surgical Treatment. By Jay Justin Older. New York, Raven Press, 1987. 133 pages, index, illustrated $74.50

Reviewed by JEFFREY A. NERAD
Iowa City, Iowa

Intended to assist the clinician with the proper diagnosis and treatment of the patient with an eyelid lesion, this text is a valuable resource for the practitioner with a special interest in eyelid lesions.

The book is divided into two major sections, Diagnosis and Treatment of Eyelid Tumor, and Anatomy and Reconstruction of the Eyelids. The first section contains a comprehensive discussion of benign and malignant tumors. Points to guide clinical recognition are stressed. Representative clinical photographs demonstrate features of most lesions described. Histopathologic descriptions and photomicrographs are not included. The written summaries of eyelid lesions are succinct and accurate. Basal cell, squamous cell, and sebaceous cell carcinoma are discussed in detail. A general scheme for eyelid tumor treatment using surgical excision with the Mohs' technique or frozen section control is explained. Radiation therapy and cryotherapy are briefly mentioned.

The second section deals with eyelid anatomy of interest to the reconstructive surgeon and with surgical techniques useful for specific eyelid defects. The anatomy portion is helpful for those unfamiliar with eyelid anatomy and serves as a useful review for those well acquainted with the normal eyelid. Separate chapters discuss defects involving the lower eyelid, upper eyelid, canthi, and anterior lamella. Each chapter contains general principles of eyelid repair and explains the author's choice of eyelid repair for specific portions of the eyelid.

The topics covered are well organized and appropriate to the intent of the book. The color photographs are generally of high quality; however, those in the first section are often not of high enough magnification to allow identification of tumor detail. The diagrams are clear and instructive. The reference lists will be helpful for those readers seeking more information. After studying the photographs and text, the practitioner should be able to recognize most eyelid tumors. With the help of the diagrams, one should be able to excise most lesions and reconstruct most defects using simple and moderately complex procedures.

For those general ophthalmologists interested in a text focusing on the clinical diagnosis and treatment of eyelid lesions, this book will do nicely.

Books Received

Pocket Atlas of Cranial Magnetic Resonance Imaging. By Victor M. Haughton and David L. Daniels. New York, Raven Press, 1986. Softcover, 61 pages, illustrated. $12.50

Ophthalmologists who want to look carefully at the magnetic resonance scans of their own patients should start with this little book. There are about 50 contiguous 5-mm magnetic resonance slices of normal brains (22 axial, 23 coronal, and five sagittal slices). All of them are T_2-weighted, that is, with bright spinal fluid. Six or seven anatomic features are labeled in each photograph.

Boletin del Instituto Nacional de Investigaciones Oftalmologicas, Vol. V. Edited by Edward Grom and Leon Broitman. Caracas, Instituto Nacional de Investigaciones Oftalmologicas, 1987. 901 pages, illustrated.

Many of the papers in this substantial volume are on the psychophysiology of vision and the history of ophthalmology.

ABSTRACT DEPARTMENT

Edited by David Shoch, M.D.

Acta Ophthalmologica

A simple clinical method of assessing patients with optic nerve hypoplasia. The disc-macula distance to disc diameter ratio (DM/DD). Wakakura, M., and Alvarez, E. (Dept. Ophthalmol., School of Med., Kitasato Univ., 1-15-1 Kitasato, Sagamihara, Kanagawa, 228 Japan). Acta Ophthalmol. 65:612, 1987.

The authors made three measurements of fundus photographs to determine a ratio that identifies small optic nerves in optic nerve hypoplasia. One half of the average of the vertical and horizontal diameters of the disk, the mean disk diameter, was added to the measurement from the edge of the disk to the fovea centralis to give a disk-macula distance. The ratio of these two measurements, the disk-macula distance divided by the disk diameter, averaged 3.25 ± 0.26 in 11 patients with optic nerve hypoplasia. There was no statistical difference between men and women and between right and left eyes. In 58 eyes of 48 normal subjects, the ratio was 2.67 ± 0.19; in 22 eyes of 11 patients with primary open-angle glaucoma, it was 2.61 ± 0.18; and in 25 eyes of 16 patients with optic atrophy, it was 2.63 ± 0.22. The difference between these three groups and the group with optic nerve hypoplasia was significant ($P < .001$). (3 figures, 1 table, 13 references) —David Shoch

American Journal of Medical Genetics

Prenatal diagnosis of retinal detachment in Walker-Warburg syndrome. Farrell, S. A., Toi, A., Leadman, M. L., Davidson, R. G., and Caco, C. (Div. Genet., Credit Valley Hosp., 2200 Eglinton Ave. W., Mississauga, Ontario, Canada L5M 2N1). Am. J. Med. Genet. 28:619, 1987.

Ultrasonography in a pregnant woman, who had previously delivered a healthy daughter, suggested local hydrocephalus. Repeat ultrasonography disclosed an unusual ocular finding that was interpreted as a retinal detachment. This finding, along with the associated hydrocephalus, suggested the diagnosis of Walker-Warburg syndrome and the pregnancy was terminated. The autopsy confirmed the diagnosis. (4 figures, 10 references)—David Shoch

Deletion (13) (q14.1q14.3) in two generations. Variability of ocular manifestations and definition of the phenotype. Wilson, W. G., Campochiaro, P. A., Conway, B. P., Carter, B. T., Sudduth, K. W., Watson, B. A., and Sparkes, R. S. (Dept. Pediatr., Univ. Virginia Med. Ctr., Charlottesville, VA 22908). Am. J. Med. Genet. 28:675, 1987.

In one family, a girl with deletion in the long arm of chromosome 13 had unilateral retinoblastoma, whereas her sister and brother were shown to have exactly the same deletion but no retinoblastomas. However, these two siblings did show retinal colobomata. Therefore, the deletion of 13q14 does not necessarily indicate the presence of retinoblastoma, but it does indicate the likelihood of ocular abnormalities. (3 figures, 2 tables, 18 references)—David Shoch

Archives of Dermatology

Hypertrichosis of the eyelashes in acquired immunodeficiency syndrome. Cassanova, J. M., Puig, T., and Rubino, M. (Dept. Med., Hospital Arnau de Vilanova, Rovira Roure 80, 25006 Lleida, Spain). Arch. Dermatol. 123:1599, 1987.

Three young men with the acquired immunodeficiency syndrome had unusually long eyelashes as well as some increase in the length of eyebrow hair. None of the patients was suffering from the other diseases that are sometimes

associated with excessive eyelash length, such as porphyria or hypothyroidism, nor was there any history of intake of drugs associated with hypertrichosis such as phenytoin, corticosteroids, psoralen, or cyclosporine. Hypertrichosis appears to be another skin manifestation of the acquired immunodeficiency syndrome. (2 figures, 2 tables, 4 references) —David Shoch

Binocular Vision

Inferior oblique recession to the (adjacent) vortex vein. A report of 341 operations. Hered, R. W., Ying-Fen, Z., Hiles, D. A., and Gardner, T. A. (Dept. Ophthalmol., Univ. Pittsburgh, Pittsburgh, PA 15213). Binocul. Vision 3:23, 1988.

In 336 consecutive patients with varying degrees of inferior oblique overaction, 528 ungraded inferior oblique muscle recessions to the inferior temporal vortex vein were performed. After appropriate exclusion for cause, results of 341 operations were analyzed. Two years postoperatively, the undercorrection rate was 13%. Three to 12 years postoperatively, the undercorrection rate rose to 21%. Reoperations were required in 6% of the eyes and recurrent overaction resolved spontaneously in 7% of cases. The overcorrection rate was 1%. This procedure appears equally effective, but not more effective, than other routine inferior oblique muscle weakening procedures such as disinsertion, intermediate segmental myectomy and myotomy, and simple recession without anterior transposition. (4 figures, 1 table, 20 references)—Paul E. Romano

British Journal of Ophthalmology

Eyes or patients? Traps for the unwary in the statistical analysis of ophthalmological studies. Newcombe, R. G., and Duff, G. R. (Dept. Med. Computing and Statistics, Univ. Wales College of Med., Heath Pk., Cardiff, Wales CF4 4XN). Br. J. Ophthalmol. 71:645, 1987.

In reports on ophthalmological research the results of measurements on the eye are often expressed as mean and standard deviation based on m patients, n eyes ($n > m$). This approach leads to t tests that are invalid because the measurements on the two eyes of one subject are usually related, not independent. In a simulation study involving intraocular pressure data analysed in this way, the null hypothesis of no difference between groups was rejected at a nominal alpha = 0.05 level in 39 out of 200 simulations; thus the true alpha was nearly 0.2. This approach is excessively prone to produce false positive results. (2 references) —Authors' abstract

Characterisation of ocular melanoma with cutaneous melanoma antibodies. Bomanji, J., Garner, A., Prasad, J., Albert, D. M., Hungerford, J. L., Granowska, M., and Britton, K. E. (Dept. Nuclear Med., St. Bartholomew's Hosp., West Smithfield, London, England EC1A 7BE). Br. J. Ophthalmol. 71:647, 1987.

In this preliminary study on characterizing a monoclonal antibody specific for ocular melanoma, three cutaneous melanoma monoclonal antibodies were used as well as immunofluorescent staining on cultured ocular melanoma cell lines and on cell impressions made from fresh ocular melanoma cells obtained from six patients. A further test was done of the avidin-biotin technique, but it proved unsatisfactory because of the melanin present in three of the tumors. Three monoclonal antibody preparations were positive in melanomas with a dominant epithelioid cell type or a dominant spindle cell type. These may be suitable for imaging ocular melanomas after labeling with iodine-123, technetium-99m, or indium-111. (1 figure, 1 table, 16 references)—David Shoch

Cytological factors relating to posterior capsule opacification following cataract surgery. Jacob, T. J. C., Humphry, R. C., Davies, E. G., and Thompson, G. M. (West of England Eye Infirm., Magadelen St., Exeter, England). Br. J. Ophthalmol. 71:659, 1987.

Simulated extracapsular cataract extractions on cadaver eyes were performed which demonstrated that the cells of the anterior capsule remain largely intact and that only a small

amount of cortical lens matter remains postoperatively. Human lens epithelial cells from normal and cataractous lenses were grown in culture. There was no appreciable difference in growth rate between cells from normal and those from cataractous lenses or between equatorial and central capsule cells. The cells grew from the cut edges of the capsule, suggesting that release from contact inhibition is an important factor in stimulating proliferation. The daughter cells became increasingly abnormal and metaplastic in successive generations, but there was no evidence of differentiation into fibroblasts within the 35-day culture period, suggesting that a retinal growth factor may be involved with the fibrosis occurring in opacification of the posterior capsule. A small anterior capsulotomy will release fewer cells from contact inhibition and hence reduce cell proliferation after extracapsular cataract extraction. (3 figures, 15 references)—Authors' abstract

Journal of the American Academy of Dermatology

Safety parameters for avoiding acute ocular damage from the reflected CO_2 (10 μm) laser beam. Friedman, N. R., Saleeby, E. R., Rubin, M. G., Sandu, T., and Krull, A. (Bay Area Dermatology, 3537 West Front St., Traverse City, MI 49684). J. Am. Acad. Dermatol. 17:815, 1987.

Unfocused reflected CO_2 laser light can produce corneal damage, especially when used at high-power densities. The authors found that it is safer to use anodized instruments, which reduce reflection. People working in the vicinity of CO_2 lasers must wear wrap-around plastic or glass spectacles. (5 figures, 8 references)—David Shoch

JAMA

Bilateral optic neuropathy and osteolytic sinusitis. Complications of cocaine abuse. Newman, N. M., DiLoreto, D. A., Ho, J. T., Klein, J. C., and Birnbaum, N. S. (Dept. Ophthalmol., Pacific Presbyterian Med. Ctr., P.O. Box 7999, San Francisco, CA 94120). J.A.M.A. 259:72, 1988.

A 43-year-old man with a 15-year history of daily intranasal cocaine use developed "holes in his vision." Examination showed that visual acuity in the right eye was normal, but was reduced to 20/70 in the left eye. The patient had a relative afferent pupillary defect in his left eye. Ophthalmoscopy showed slight swelling of the right optic nerve head and marked edema and hyperemia of the left optic nerve. A centrocecal defect was present in the right eye on Goldmann visual field testing as was an altitudinal defect in the left eye. Magnetic resonance imaging showed extensive bony destruction of the nasal cavity, paranasal sinuses, and the floor of the anterior cranial fossa. A diagnosis was made of osteolytic sinusitis, with secondary bilateral optic nerve involvement. Four months later, after cessation of nasal cocaine intake, the patient's visual acuity and visual field defects had stabilized. The general appearance of the disease is that of a midline granuloma syndrome. In this patient the compelling clinical history and the absence of specific histopathologic findings led to the exclusion of idiopathic midline destructive disease. (4 figures, 20 references)—David Shoch

Lasers in Surgery and Medicine

Safety of high-energy neodymium:YAG laser pulses in YAG sclerostomy. March, W. F., Gherezghiher, T., Shaver, R. P., Koss, M. C., and Nordquist, R. E. (Dean McGee Eye Inst., 608 Stanton L. Young Blvd., Oklahoma City, OK 73104). Lasers Surg. Med. 6:584, 1987.

YAG laser sclerostomy was performed in 15 eyes of nine cynomolgus monkeys to determine whether the power used to create a permanent drainage fistula from the anterior chamber to the subconjunctival space could be safely increased in primate eyes. Individual pulse energies ranged from 10 to 135 mJ, and the total pulse energy ranged from 2,000 to 3,600 mJ. The eyes of six monkeys were removed within one hour after completing the procedure. The three remaining animals were observed for

three to six months, with frequent measurements of intraocular pressure. The eyes were then removed and fixed. Histologic examination by light microscopy or scanning and transmission electron microscopy of the corneal endothelium, lens capsule, iris, ciliary body, retina, and sclera failed to show any damage. The authors conclude that in the primate eye, pulse energies of up to 135 mJ are tolerated, with no evidence of damage distant from the sclerostomy site or from the shock wave. (6 figures, 8 references)—David Shoch

Nature

Perception of shape from shading. Ramachandran, V. S. (Univ. California, San Diego, CA 92093). Nature 331:163, 1988.

The author used a series of circles with shading to show that simple shading can cause a three-dimensional effect, which is largely related to the assumption by the eye that light comes from only one direction. When the lighting was from above, almost all the round circles looked like spheres bulging out of the page. When the lighting was from below, the circles appeared like holes in the page. When the circles were shaded differently, the eye segregated some as spheres and some as holes. This effect was less obvious with light coming from the left or right, but if two rows of circles were shown, one row being shaded on the left and one on the right, the eye did not accept both rows as spheres or holes but assigned a different contour to each row depending on the source of the light. The perception of shape from shading is a global operation that allows for only one light source illuminating the entire visual image. Three-dimensional shapes that are made by shading can provide the appearance of apparent motion. (4 figures, 17 references)—David Shoch

Neurosurgery

Are flash-evoked visual potentials useful for intraoperative monitoring of visual pathway function? Cedzich, C., Schramm, J., and Fahlbusch, R. (Univ. Erlangen-Nürnberg, Schwabachanlage 6, 8520 Erlangen, West Germany). Neurosurgery 21:709, 1987.

To evaluate whether visual-evoked potentials might be useful in indicating that damage was occurring to the optic nerve, chiasm, or tracts during neurosurgery, the authors measured flash-evoked visual potentials from the scalp in 35 patients with tumors along the visual pathway. They found numerous changes in the visual potentials during surgery, but none of them could be correlated with later impairment of visual function. In only one patient with a decrease of visual acuity from 0.4 to 0.3 was there a concomitant intraoperative potential loss. Generally, the flash-evoked visual potentials appear too early and too prominently in the course of surgery to be caused solely by manipulation of the optic pathways. Flash-evoked potentials are not recommended as a suitable way to monitor visual function during neurosurgery. (4 figures, 4 tables, 25 references)—David Shoch

Down-beat nystagmus. Case report with magnetic resonance imaging and surgical treatment. Pinel, J. F., Larmande, P., Guegan, Y., and Iba-Zizen, M. T. (Dept. Neurol., Centre Hospitalier Universitaire Bretonneau, 37044 Tours Cedex, France). Neurosurgery 21:736, 1987.

A 36-year-old woman was examined in April 1985 for complaints of oscillopsia and decreased visual acuity. Her illness began in 1974 with vertical diplopia. A nystagmus developed in 1976. Results of computed tomography in 1979 were normal. In 1980 she first experienced oscillopsia. In 1985 the nystagmus was coarse and regular, with a slow phase upward and a fast phase downward. The intensity was increased in lateral gaze. Magnetic resonance imaging showed an extensive cystic lesion limited to the medulla. Incision and aspiration of the cyst resulted in subsequent improvement in visual acuity and disappearance of the oscillopsia and diplopia. The oscillopsia has not recurred. In primary position the eyes are now stable, but a slight counterclockwise rotary nystagmus is occasionally noted. (1 figure, 40 references)—David Shoch

New England Journal of Medicine

Prediction of the risk of hereditary retinoblastoma, using DNA polymorphisms within the retinoblastoma gene. Wiggs, J., Nordenskjold, M., Yandell, D., Rapaport, J., Grondin, V., Janson, M., Werelius, B., Petersen, R., Craft, A., Riedel, K., Liberfarb, R., Walton, D., Wilson, W., and Dryja, T. P. (Massachusetts Eye and Ear Infirm., 243 Charles St., Boston, MA 02114). N. Engl. J. Med. 318:151, 1988.

The authors devised a method to identify children with a family history of retinoblastoma who have a mutant allele, which thus eliminates the need for examination of those children found to have a normal genotype. They identified restriction fragment length polymorphisms within the retinoblastoma gene in 20 families with members who had hereditary retinoblastoma. In 18 kindreds they demonstrated a consistent association of marker restriction fragment length polymorphisms with the mutation predisposing to retinoblastoma. (5 figures, 3 tables, 25 references)—David Shoch

Retina

Non-Hodgkin's lymphoma causing fundus picture simulating fundus flavimaculatus. Gass, J. D. M., Weleber, R. G., and Johnson, D. R. (Bascom Palmer Eye Inst., P.O. Box 016880, Miami, FL 33101). Retina 7:209, 1987.

Two healthy patients without systemic complaints had visual loss and a peculiar flecked retina, similar in appearance to fundus flavimaculatus. In one patient, results of a medical examination for a reticulum cell sarcoma were normal. One year later the patient developed anorexia, fever, and lymphadenopathy. Results of biopsy of the supraclavicular nodes showed a non-Hodgkin's large cell lymphoma. The second patient had a similar course, but his systemic findings appeared four months after the retinal lesions were noted. Results of a lymph node biopsy showed a non-Hodgkin's large cell lymphoma. Generally non-Hodgkin's large cell malignant lymphoma, sometimes called reticulum cell sarcoma, tends to occur in the eye in association with central nervous system involvement. The systemic form usually involves the reticuloendothelial system and rarely the eye. In these two patients the disease was systemic, but involved the eyes and not the central nervous system. These retinal changes must have been caused by an invasion of the choroid, with damage to the overlying pigment epithelium. (3 figures, 24 references)—David Shoch

NEWS ITEMS

Send News Items to
Editor
American Journal of Ophthalmology
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Chicago, IL 60611

The Journal invites information concerning meetings, postgraduate courses, lectures, honors, and appointments. Double space each item and provide the name and address of the responsible author. Announcements of courses, meetings, and lectures must be submitted at least six months before the date of the event.

Eye Hospital Rotterdam: Third Course: Silicone Oil in Vitreoretinal Surgery

The Eye Hospital Rotterdam will present the Third Course, Silicone Oil in Vitreoretinal Surgery, Sept. 12 and 13, 1988, in Rotterdam, The Netherlands. For further information, write Dorine Verhoeven, Course Secretary, Eye Hospital Rotterdam Schiedamsevest 180, 3000 LM Rotterdam, The Netherlands.

Fourth International Symposium of The Northern Eye Institute

The Northern Eye Institute will sponsor Glaucoma, the Fourth International Symposium, July 14–16, 1988, in Manchester, England. For further information, write Dr. R. P. F. Gregory, Department of Biochemistry and Molecular Biology, The Medical School, Oxford Road, Manchester M13 9PT, England.

International Society for Ophthalmic Ultrasound

The International Society for Ophthalmic Ultrasound will hold its meeting Aug. 28–Sept. 2, 1988, in Iguazu Falls, Argentina. For further information, write Prof. Dr. Roberto Sampaolesi, Parana 1239, 1° Piso, 1018 Buenos Aires, Argentina.

Intraocular Lens Convention

The Eye Research Centre will present an Intraocular Lens Convention, Jan. 4–5, 1989. For further information, write Dr. Chander Neroor, Director, Dr. Agarwal's Eye Institute, 13, Cathedral Road, Madras 600 086, India.

American Academy of Ophthalmology: 1988 Annual Meeting

The Annual Meeting of the American Academy of Ophthalmology will be held Oct. 8–12, 1988, in Las Vegas, Nevada. For further information, write Meetings Department, American Academy of Ophthalmology, P.O. Box 7424, San Francisco, CA 94120.

Cornell University: Quantitative A- and B-Scan Ultrasonography and Diagnostic Imaging of the Eye and Orbit

Cornell University will hold a course, Quantitative A- and B-scan Ultrasonography and Diagnostic Imaging of the Eye and Orbit, June 2 and 3, 1988, in New York, New York. For further information, write Mary P. Whalen, Course Coordinator, USG '88, Cornell University, 525 E. 68th St., New York, NY 10021.

Cornell University: Therapeutic Ultrasound in the Treatment of Glaucoma and Malignant Tumors

Cornell University will hold a course, Therapeutic Ultrasound in the Treatment of Glaucoma and Malignant Ttumors, June 24 and 25, and Oct. 28 and 29, 1988. For further information, write Mary P. Whalen, Cornell University, 525 E. 68th St., New York, NY 10021.

The Eye Institute and the Wisconsin Academy of Ophthalmology: Current Problems in Ophthalmology

The Eye Institute and the Wisconsin Academy of Ophthalmology will sponsor Current Problems in Ophthalmology, June 10–12, 1988, in Kohler, Wisconsin. For further information, write The Eye Institute, Medical College of Wisconsin, Milwaukee County Medical Complex, 8700 W. Wisconsin Ave., Milwaukee, WI 53226.

Johns Hopkins Medical Institutions: Principles of Data Collection, Data Management, and Data Analysis for Clinical Trials

The Johns Hopkins Medical Institutions will sponsor a course, Principles of Data Collection, Data Management, and Data Analysis for Clinical Trials, June 9 and 10, 1988, in Baltimore,

Maryland. For further information, write Francette Boling, Program Coordinator, The Johns Hopkins Medical Institutions, 720 Rutland Ave., Turner 22, Baltimore, MD 21205.

Lighthouse and Gerontological Society: Age-Related Vision Loss Symposium

The Lighthouse and Gerontological Society will sponsor a symposium, Age-Related Vision Loss: Developments in Low Vision Practice and Research, July 18 and 19, 1988, in New York, New York. For further information, write Francine Leinhardt, Conference Coordinator, 210 E. 64th St., New York, NY 10021.

Phillips Eye Institute: Twelfth Annual Current Trends in Ophthalmology

Phillips Eye Institute will sponsor the Twelfth Annual Current Trends in Ophthalmology, Nov. 19, 1988, in Minneapolis, Minnesota. For further information, write Susan Allen, Coordinator, Phillips Eye Institute, 2215 Park Avenue South, Minneapolis, MN 55404.

Retina Consultants: Pneumatic Retinopexy Symposium

Retina Consultants will sponsor a Pneumatic Retinopexy Symposium, Aug. 5–6, 1988, in San Diego, California. For further information, write Patti Gurerro, Retina Consultants, 12630 Monte Vista Rd., #104, Poway, CA 92064.

Retina Research Foundation: Retina Update

The Retina Research Foundation will sponsor a seminar, Retina Update, April 23, 1988, in New Orleans, Louisiana. For further information, write Kurt A. Gitter, M.D., Retina Research Foundation, 1413 Delachaise St., New Orleans, LA 70115.

Rush Presbyterian-St. Luke's Medical Center: Corneal Surgery for the Anterior Segment Surgeon

Rush Presbyterian-St. Luke's Medical Center will sponsor a course, Corneal Surgery for the Anterior Segment Surgeon, June 24 and 25, 1988, in Chicago, Illinois. For further information, write Rush Presbyterian-St. Luke's Medical Center, Office of Continuing Medical Education, 600 S. Paulina, Chicago, IL 60612.

University of Illinois: Contact Lens Course

The University of Illinois at Chicago will sponsor a Contact Lens Course, June 17–18, 1988, in Chicago, Illinois. For further information, write Conference Registrar, The University of Illinois at Chicago, Conferences and Institutes (M/C 607), Second Floor North, 912 S. Wood St., Chicago, IL 60612.

University of Michigan: 60th Annual Ophthalmology Spring Conference

The University of Michigan will sponsor a course, Current Concepts in Glaucoma: 60th Annual Ophthalmology Spring Conference, May 20 and 21, 1988, in Ann Arbor, Michigan. For further information, write Arlene Bradford, Office of Continuing Medical Education, Towsley Center-Box 0201, University of Michigan Medical School, Ann Arbor, MI 48109-0201.

University of Pennsylvania Scheie Eye Institute: Certification Review Course for Ophthalmic Assistants and Technicians

The University of Pennsylvania will sponsor a Certification Review Course for Ophthalmic Assistants and Technicians, June 2–4, 1988, in Philadelphia, Pennsylvania. For further information, write Mary Allegrini, University of Pennsylvania, Scheie Eye Institute, 51 N. 39th St., Philadelphia, PA 19104.

Wills Eye Hospital: Seventh Biennial Cornea Conference

Wills Eye Hospital will present the Seventh Biennial Cornea Conference, A Practical Approach to Corneal and External Diseases, Nov. 4 and 5, 1988, in Philadelphia, Pennsylvania. For further information, write Lucia M. Manes, Conference Coordinator, Wills Eye Hospital, Department of Continuing Education, 9th and Walnut Sts., Philadelphia, PA 19107.

National Children's Eye Care Foundation: Research and Fellowship Support Funds in Pediatric Ophthalmology

The National Children's Eye Care Foundation announces loan and grant support in pediatric ophthalmology. Annual interest-free loans of up to $10,000 are available for training conducted in North America. Priority consideration is given to fellows who seek support for additional training after completion of a one-

year fellowship program in pediatric ophthalmology and strabismus and to fellows who plan to pursue academic or teaching careers after completion of fellowship training. Consideration will also be given to the relative needs of the population to be served by the fellow upon completion of training. Request for a fellowship loan will be considered after notification of acceptance to a North American training program has been received by the applicant.

Grants for investigations in North America in pediatric ophthalmology are available. Loan and Grant applications must be submitted by April 30, 1988 to be considered for these annual awards. For applications and further information, write National Children's Eye Care Foundation, Suite 700, 1101 Connecticut Ave. N.W., Washington, DC 20036.

Research to Prevent Blindness: Senior Scientific Investigators

Research to Prevent Blindness announced special funding for ten scientists whose concepts and records of achievement have contributed significantly to eye research. Each will receive $40,000 to advance clinical and basic studies.

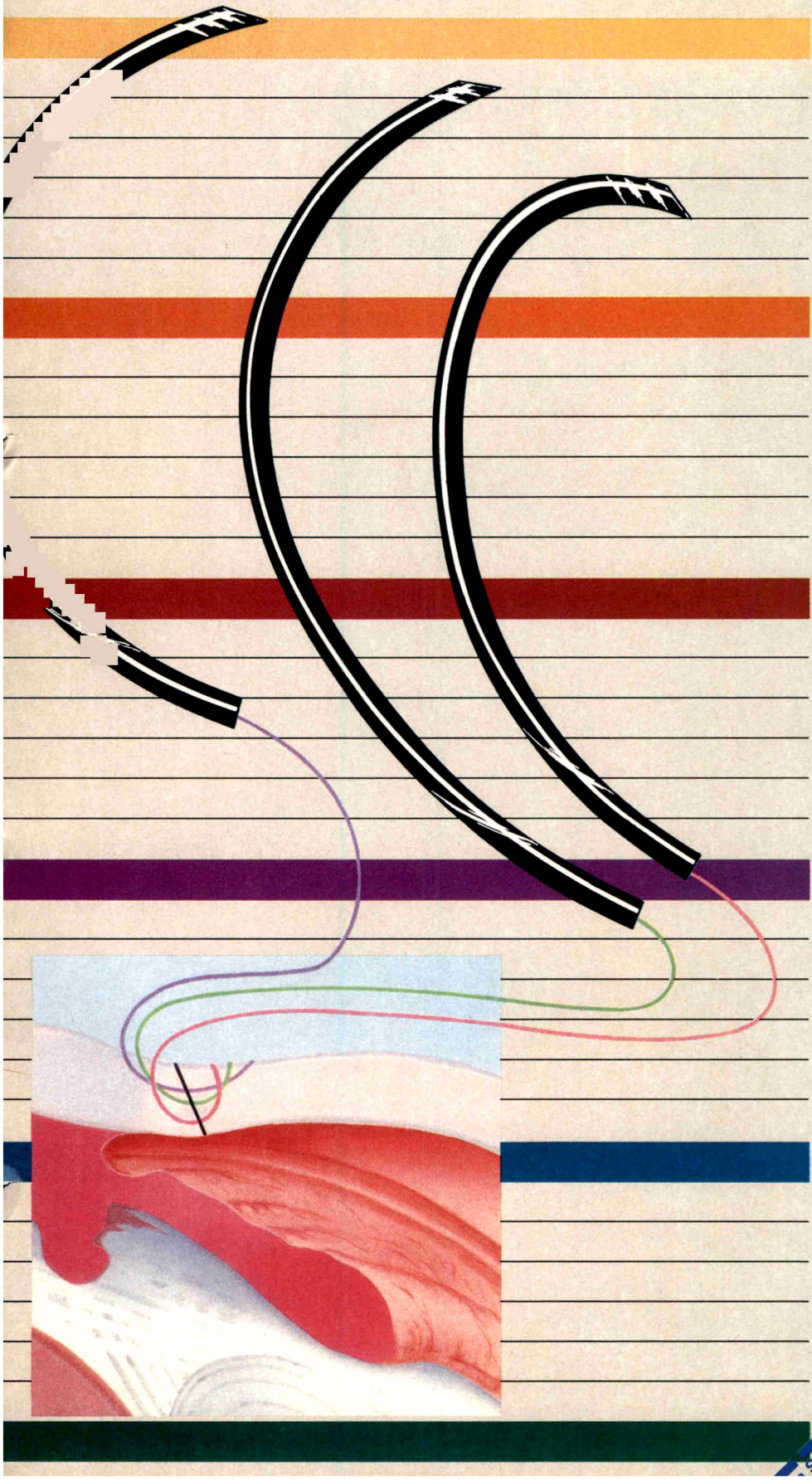
Named as RPB senior scientific investigators are: Matthew Alpern, Ph.D., University of Michigan; Oscar A. Candida, M.D., Mount Sinai School of Medicine; Lynette Feeney-Burns, Ph.D., University of Missouri-Columbia School of Medicine; Douglas E. Gaasterland, M.D., Georgetown University School of Medicine Diane L. Hatchell, Ph.D., Duke University School of Medicine; Matthew M. LaVail, Ph.D., University of California, San Francisco School of Medicine; Robert F. Miller, M.D., Washington University School of Medicine; Denis M. O'Day, M.D., Vanderbilt University School of Medicine; Harry A. Quigley, M.D., Johns Hopkins University School of Medicine; and Samuel Sokol, M.D., Tufts University School of Medicine.

Personal

Stephen A. Obstbaum

Stephen A. Obstbaum has been named director of ophthalmology at Lenox Hill Hospital. His appointment became effective Jan. 4, 1988.

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"The Video Advantage," a recently released publication of Milner-Fenwick, Inc., is a step-by-step guide on using videos to improve patient education, doctor/patient rapport, office work flow, and informed consent documentation. The booklet addresses the questions most frequently asked by health professionals concerning the use of patient education videotapes.

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Low Vision Aids

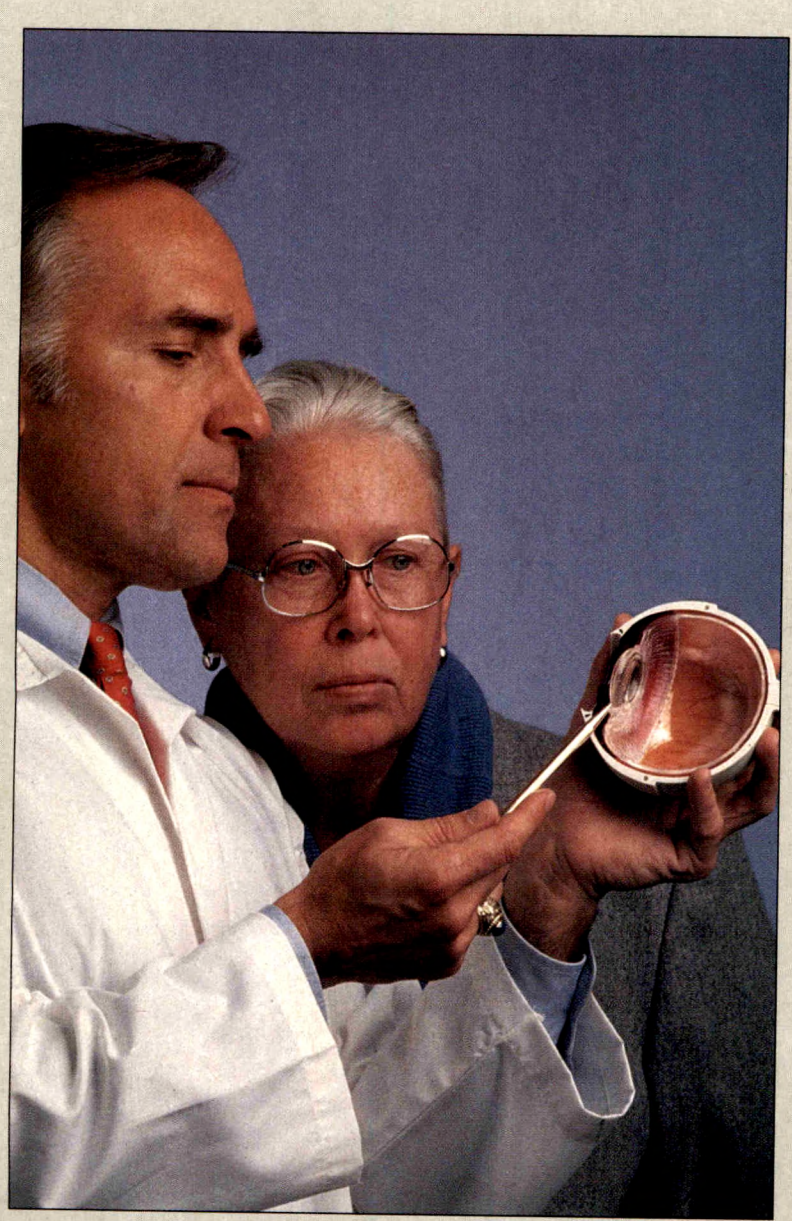
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IBM has introduced the IBM Personal System/2 Screen Reader keypad, which allows blind or visually impaired users greater access to the IBM Personal System/2 family of products and related software programs. The user hears the text displayed on the screen. It is the first member of the IBM Independence Series of products designed for computer users with special needs.

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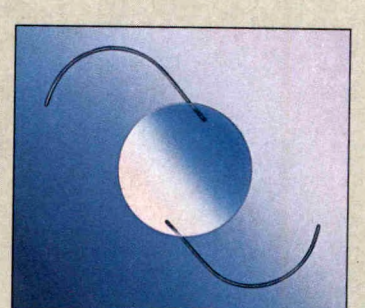
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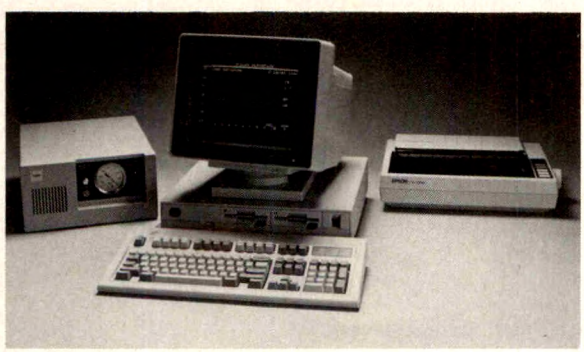
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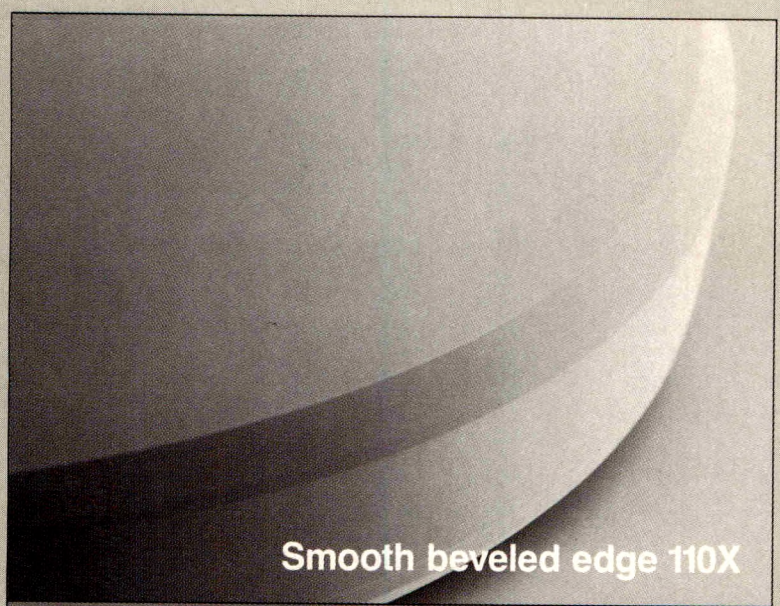


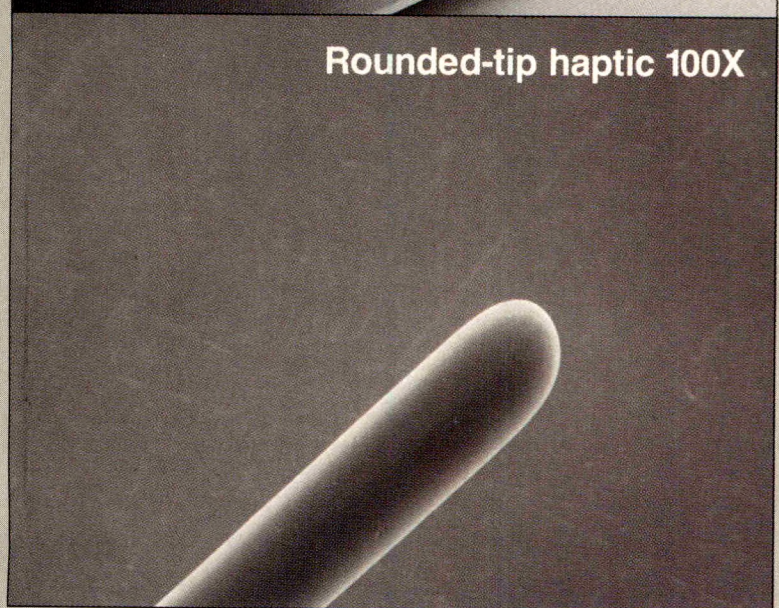
A new system that converts photographic images to a television image has been introduced by Tamron Industries, Inc. The new unit, called the FOTOVIX Film-Video Processor, converts either negative or positive, color or black and white photographic images to an NTSC video signal so that they can be viewed on a television screen or monitor. The images can also be recorded onto any type of video tape.

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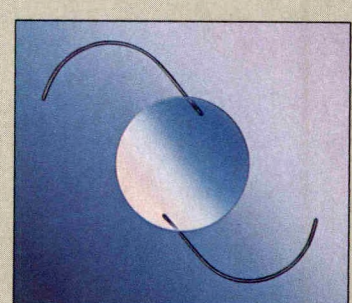
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Seiko Optical Products, a manufacturer of spectacle lenses, has introduced an antireflective demonstration kit to assist dispensers in explaining the benefits of AR lenses to consumers. An effective marketing tool for optical professionals, the single lens demonstration kit shows patients and customers the advantages of AR coating over uncoated lenses. Seiko also offers a two-year written guarantee against scratches and coating defects on all of its Diacoat lenses.

The demonstration kit may be purchased for $12 or is available at no cost when making multiple AR lens purchases.

Lasers

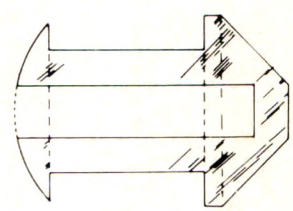
Scott Medical Products
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Scott Medical Products now manufactures a complete line of pure gases and gas mixtures for consistent, trouble-free operation of medical lasers. Laser gases are gravimetrically manufactured using high purity component gases. The blend tolerance is ±0.05% absolute to ensure consistent laser power. In addition to standard laser mixtures, custom laser mixtures can be blended.

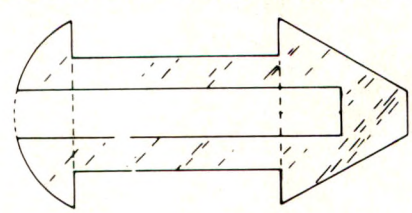
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Memphis, TN 38119
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NEW MODEL #0003 PLUG



STANDARD MODEL #0001 PLUG



Eagle Vision, Inc., has introduced its newest dry eye product, the Eagle Vision-Freeman Punctum Plug Kit, featuring two short plugs with reduced dome configuration. This new kit is in response to requests for a smaller dome and shorter length plug. These plugs also may be more suitable for smaller eyes. The new kit includes two medical grade silicone punctum plugs, one dilator/inserter instrument, physician and patient instructions, and a patient medical information card. The kit and contents are packaged in a sterile pouch for single patient use and are nontoxic and nonpyrogenic.



BSS®
THE ONLY SOLUTION WORTH ITS SALT

ALCON BSS® – FIRST AND FOREMOST

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BSS®
(BALANCED SALT SOLUTION, ALCON®)

DESCRIPTION: BSS® is a sterile physiological balanced salt solution of NaCl (Sodium Chloride), KCl (Potassium Chloride), $CaCl_2.2H_2O$ (Calcium Chloride), $MgCl_2.6H_2O$ (Magnesium Chloride), $C_2H_3NaO_2.3H_2O$ (Sodium Acetate), $C_6H_5Na_3O_7$ (Sodium Citrate). BSS is isotonic to the tissues of the eyes. It is a lint-free solution containing essential ions for normal cell metabolism. Each ml contains Sodium Chloride 0.64%, Potassium Chloride 0.075%, Calcium Chloride 0.048%, Magnesium Chloride 0.03%, Sodium Acetate 0.39%, Sodium Citrate 0.17%, Sodium Hydroxide and/or Hydrochloric Acid (to adjust pH), and Water for Injection.
CLINICAL PHARMACOLOGY: A physiologic irrigating solution.
INDICATIONS AND USAGE: For irrigation during various surgical procedures of the eyes, ears, nose, and/or throat.
WARNINGS: If blister or paper backing is damaged or broken, sterility of the enclosed bottle cannot be assured. Open under aseptic conditions only.

NOT FOR INJECTION OR INTRAVENOUS INFUSION.

PRECAUTIONS: This solution contains no preservative and should not be reused. Prior to use check the following: tip should be firmly in place, irrigating needle should be properly seated; squeeze out several drops before inserting into anterior chamber. The needle should be removed from the anterior chamber prior to releasing pressure to prevent suction.
ADVERSE REACTIONS: When the corneal endothelium is abnormal, irrigation or any other trauma may result in bullous keratopathy.
DOSAGE AND ADMINISTRATION: The adapter plug is designed to accept an irrigating needle. Tissues may be irrigated by attaching the needle to the Drop-Tainer® bottle as explained below. External irrigation may be done without the irrigating needle.
Method of using Adapter Plug for Luer-Lok® Hub Ophthalmic Irrigating Needle:
1. Aseptically remove Drop-Tainer® bottle from blister by peeling paper backing.
2. Snap on surgeon's irrigator needle. Push until firmly in place and twist.
3. Test assembly for proper function before use.

NOTE: Luer-Lok is a registered trademark of Becton, Dickinson and Company.
HOW SUPPLIED: 15ml sterile Drop-Tainer® Bottle. NDC 0065-0795-15. 30ml sterile Drop-Tainer® Bottle. NDC 0065-0795-30.
STORAGE: Store under ordinary conditions at 46° to 80°F. (8° to 27°C.)

Alcon Surgical

Surgical Products Division
Alcon Laboratories, Inc.
P.O. Box 1959
Fort Worth, TX 76101
817/293-0450

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The title page is page 1. It should contain the title, a brief heading (no more than 60 characters and spaces) in the upper right hand corner, and each author's name with the highest academic degree. The departmental affiliation of each author and the institution where the study was performed should be indicated. Sponsoring organizations and grants are acknowledged on the title page. The name and mailing address of the author to whom requests for reprints should be directed must be indicated.

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Each paper must have a summary synthesizing specifically the content of the paper in no more than 150 words. The summary must be written so that it can be read independently of the text. It should include the main clinical or research data and findings but exclude speculation.

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Source Texts

THE JOURNAL recommends the following publications as guides to style, grammar, and spelling:

CBE Style Manual Committee: Council of Biology Editors Style Manual. A Guide for Authors, Editors and Publishers in the Biological Sciences, 5th ed. Bethesda, Council of Biology Editors, 1983.

The Chicago Manual of Style, 13th ed. Chicago, University of Chicago Press, 1982.

Strunk W., Jr., and White, E. B.: The Elements of Style, 3rd ed. New York, Macmillan Publishing Co., 1979.

GLAUCOMA
THE FOURTH INTERNATIONAL SYMPOSIUM OF THE NORTHERN EYE INSTITUTE
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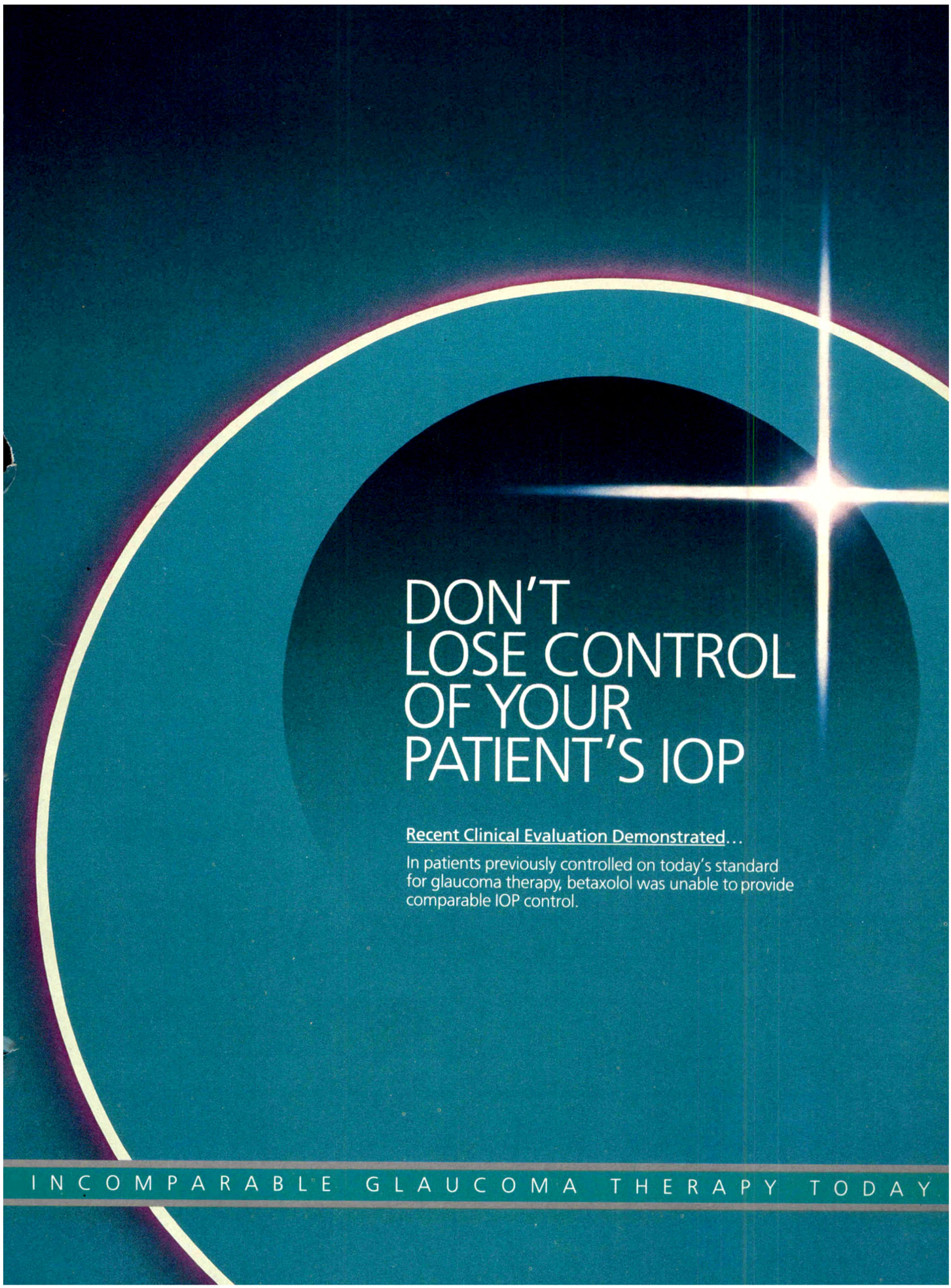
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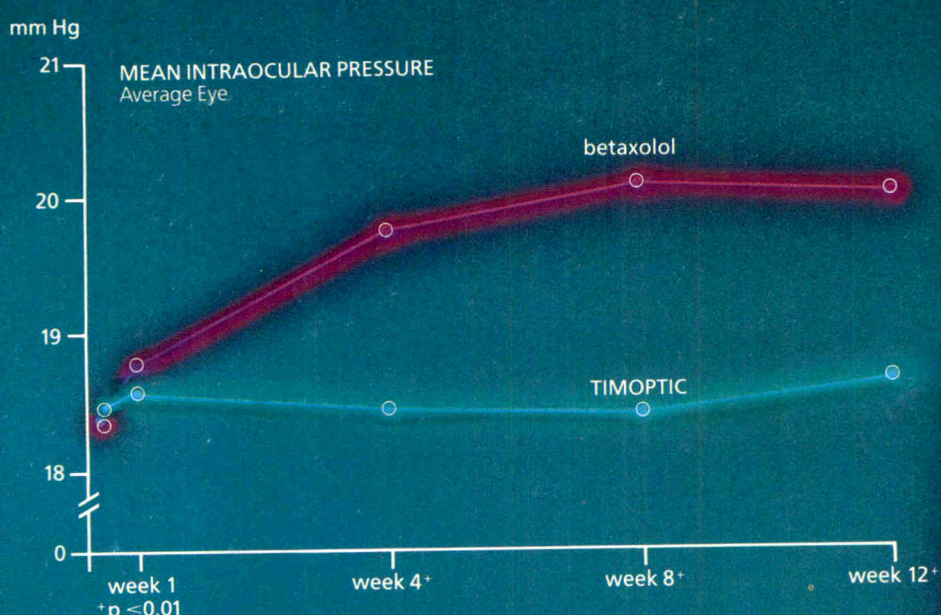

DON'T
LOSE CONTROL
OF YOUR
PATIENT'S IOP
Recent Clinical Evaluation Demonstrated...
In patients previously controlled on today's standard for glaucoma therapy, betaxolol was unable to provide comparable IOP control.
INCOMPARABLE GLAUCOMA THERAPY TODAY

DON'T LOSE CONTROL OF YOUR PATIENT'S IOP

In a multicenter study, recent clinical evaluation,[1,2] of 353 patients with a history of satisfactory IOP control and tolerability while on TIMOPTIC® (Timolol Maleate, MSD):

- Confirmed the benefits of maintaining therapy with TIMOPTIC for IOP control
- Demonstrated that TIMOPTIC surpassed Betoptic in maintaining IOP control

In patients previously controlled on TIMOPTIC, Betoptic was unable to maintain comparable IOP control:



At week 12, 97% of 149 patients on TIMOPTIC continued to be satisfactorily controlled.

At weeks 4, 8, and 12, significant increases in baseline IOP ($p \leq 0.01$) were seen in the patients treated with Betoptic.

[1]Data available upon request from Merck Sharp & Dohme, Professional Services Department, West Point, PA 19486.

[2]A total of 353 patients whose IOP was satisfactorily controlled with TIMOPTIC and in whom the drug was well tolerated were continued on TIMOPTIC 0.5% b.i.d. during a 2-week baseline period. Patients contributing data were then randomly assigned in a double-masked fashion in demographically similar groups to continue to receive either TIMOPTIC 0.5% b.i.d. (n = 149) or Betoptic 0.5% b.i.d. (n = 146). Following a baseline measurement, patients were evaluated for IOP after 1, 4, 8, and 12 weeks of therapy. In the average-eye approach, values from the right and left eye were averaged at each time point to obtain the values used in the analysis. In the worst-eye approach, the eye with the higher baseline IOP was followed throughout the course of the study.

As with the use of other antiglaucoma drugs, diminished responsiveness to TIMOPTIC after prolonged therapy has been reported in some patients. However, in one long-term study in which 96 patients have been followed for at least 3 years, no significant difference in mean IOP has been observed after initial stabilization.

TIMOPTIC is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; and hypersensitivity to any component of this product.

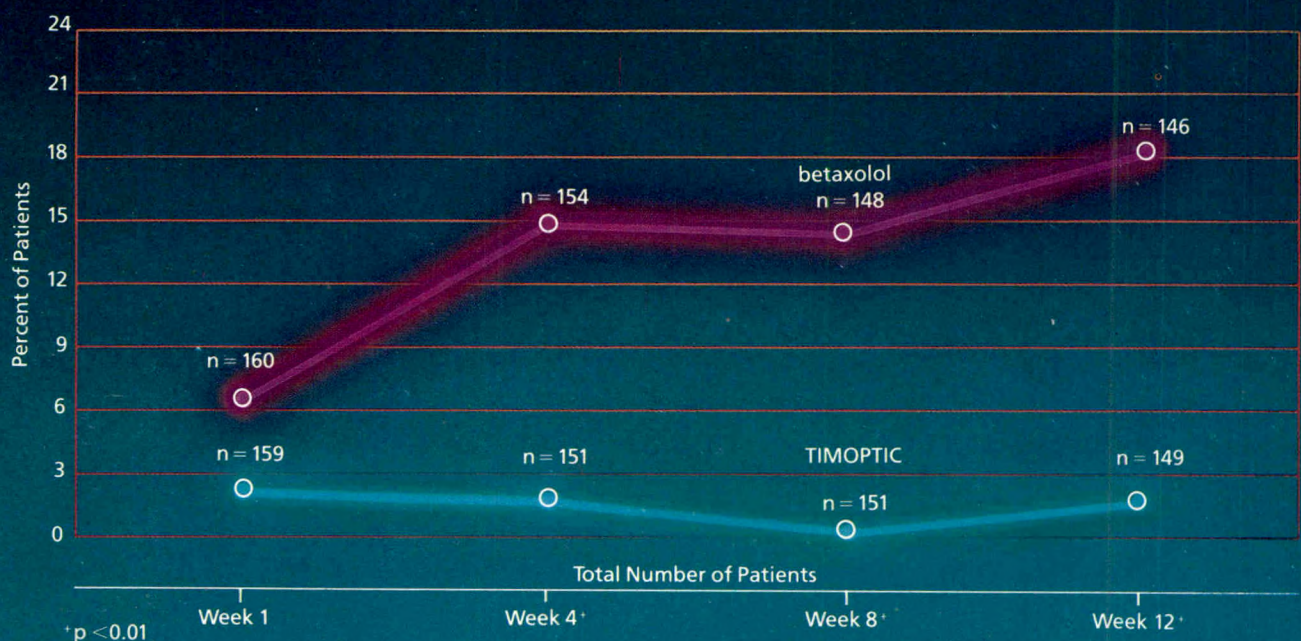
I N C O M P A R A B L E G L A

NOTE: Betoptic is the registered trademark of Alcon Laboratories, Inc. for betaxolol hydrochloride.

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PATIENTS EXHIBITING CHANGES IN INTRAOCULAR PRESSURE (FROM TREATED BASELINE) ≥ +5 mm Hg

Worst Eye



*p <0.01

Nearly 1 out of 5 patients treated with Betoptic showed an increase in IOP ≥ +5 mm Hg at week 12

For the majority of patients with chronic open-angle glaucoma or elevated IOP who are at sufficient risk to require therapy

TIMOPTIC®

(TIMOLOL MALEATE | MSD)

STERILE OPHTHALMIC SOLUTION

O M A THERAPY TODAY

Before prescribing TIMOPTIC, please see the Brief Summary of Prescribing Information on the following page.

TIMOPTIC®

(TIMOLOL MALEATE) MSD

STERILE OPHTHALMIC SOLUTION

How to start patients on TIMOPTIC:
Usual starting dosage: one drop 0.25% TIMOPTIC in the affected eye(s) twice a day.

How to transfer from another topical ophthalmic beta-adrenergic blocking agent to TIMOPTIC:
1. On the first day, after proper dosing, discontinue the topical agent being used.
2. On the second day, start treatment with one drop of 0.25% TIMOPTIC in the affected eye(s) b.i.d.

How to transfer from a single antiglaucoma agent (other than a topical ophthalmic beta-adrenergic blocking agent) to TIMOPTIC:
1. On the first day, continue with the agent already being used and add one drop 0.25% TIMOPTIC in the affected eye(s) b.i.d.
2. On the second day, discontinue the previously used agent and continue with TIMOPTIC in the affected eye(s) b.i.d.

How to transfer from several concomitantly administered antiglaucoma agents to TIMOPTIC:
1. If any agent is an ophthalmic beta-adrenergic blocker, discontinue before starting TIMOPTIC.
2. Continue the other agents being used, but add one drop of 0.25% TIMOPTIC to the affected eye(s) b.i.d.
3. On the following day, discontinue one of the other antiglaucoma agents.
4. The remaining antiglaucoma agents may be decreased or discontinued according to the patient's response to treatment.

If clinical response is not adequate:
Dosage may be increased (from the 0.25% solution) by changing to one drop 0.5% TIMOPTIC twice a day in the affected eye(s). Dosages above one drop of 0.5% TIMOPTIC twice a day generally have not been shown to produce further reduction of IOP. If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s).

In patients with a history of severe cardiac disease, signs of cardiac failure should be watched for and pulse rates should be checked.

CONTRAINDICATIONS: TIMOPTIC is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to any component of this product.

WARNINGS: As with other topically applied ophthalmic drugs, this drug may be absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death in association with cardiac failure, have been reported following administration of TIMOPTIC (see CONTRAINDICATIONS).

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, TIMOPTIC should be discontinued.

Obstructive Pulmonary Disease: PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (e.g., CHRONIC BRONCHITIS, EMPHYSEMA) OF MILD OR MODERATE SEVERITY, BRONCHOSPASTIC DISEASE OR HISTORY OF BRONCHOSPASTIC DISEASE (OTHER THAN BRONCHIAL ASTHMA OR HISTORY OF BRONCHIAL ASTHMA, IN WHICH 'TIMOPTIC' IS CONTRAINDICATED, see CONTRAINDICATIONS), SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS, INCLUDING 'TIMOPTIC'. However, if TIMOPTIC is necessary in such patients, then the drug should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution to patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

PRECAUTIONS: *General:* Patients who are receiving a beta-adrenergic blocking agent orally and TIMOPTIC should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Patients should not receive two topical ophthalmic beta-adrenergic blocking agents concurrently.

Because of potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with TIMOPTIC, alternative therapy should be considered.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. TIMOPTIC has little or no effect on the pupil. When TIMOPTIC is not alone.

As with the use of other antiglaucoma drugs, diminished responsiveness to TIMOPTIC® (Timolol Maleate, MSD) after prolonged therapy has been reported in some patients. However, in one long-term study in which 96 patients have been followed for at least three years, no significant difference in mean intraocular pressure has been observed after initial stabilization.

Drug Interactions: Although TIMOPTIC used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with TIMOPTIC and epinephrine has been reported occasionally.

Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Caution should be used in the coadministration of beta-adrenergic blocking agents, such as TIMOPTIC, and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Animal Studies: No adverse ocular effects were observed in rabbits and dogs administered TIMOPTIC topically in studies lasting one and two years respectively.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year oral study of timolol maleate in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human oral dose* (1 mg/kg/day). Similar differences were not observed in rats administered oral doses equivalent to 25 or 100 times the maximum recommended human oral dose. In a lifetime oral study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages up to 60 mg timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/mL). In Ames tests, the highest concentrations of timolol employed, 5000 or 10,000 μg/plate, were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human oral dose.

Pregnancy: Pregnancy Category C: Teratogenicity studies with timolol in mice and rabbits at doses up to 50 mg/kg/day (50 times the maximum recommended human oral dose) showed no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (1,000 times the maximum recommended human oral dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 100 times the maximum recommended human oral dose, in this case without apparent maternotoxicity. There are no adequate and well-controlled studies in pregnant women. TIMOPTIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established by adequate and well-controlled studies.

ADVERSE REACTIONS: TIMOPTIC Ophthalmic Solution is usually well tolerated. The following adverse reactions have been reported either in clinical trials of up to three years' duration prior to release in 1978 or since the drug has been marketed.

BODY AS A WHOLE: Headache, asthenia, chest pain. CARDIOVASCULAR: Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, palpitation, cardiac arrest. DIGESTIVE: Nausea, diarrhea. NERVOUS SYSTEM/PSYCHIATRIC: Dizziness, depression, increase in signs and symptoms of myasthenia gravis, paresthesia. SKIN: Hypersensitivity, including localized and generalized rash, urticaria. RESPIRATORY: Bronchospasm (predominantly in patients with preexisting bronchospastic disease), respiratory failure, dyspnea, nasal congestion. ENDOCRINE: Masked symptoms of hypoglycemia in insulin-dependent diabetics (see WARNINGS). SPECIAL SENSES: Signs and symptoms of ocular irritation, including conjunctivitis, blepharitis, keratitis, blepharoptosis, decreased corneal sensitivity, visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis.

Causal Relationship Unknown: The following adverse effects have been reported, and a causal relationship to therapy with TIMOPTIC has not been established: *Body as a Whole:* Fatigue; *Cardiovascular:* Hypertension, pulmonary edema, worsening of angina pectoris; *Digestive:* Dyspepsia, anorexia, dry mouth; *Nervous System/Psychiatric:* Behavioral changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence, and other psychic disturbances; *Skin:* Alopecia; *Special Senses:* Aphakic cystoid macular edema; *Urogenital:* Retroperitoneal fibrosis, impotence.

The following additional adverse effects have been reported in clinical experience with oral timolol maleate and may be considered potential effects of ophthalmic timolol maleate: *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Edema, worsening of arterial insufficiency, Raynaud's phenomenon, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting; *Hematologic:* Nonthrombocytopenic purpura; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating, cold hands and feet; *Musculoskeletal:* Arthralgia, claudication; *Nervous System/Psychiatric:* Vertigo, local weakness, decreased libido, nightmares, insomnia, diminished concentration; *Respiratory:* Rales, cough, bronchial obstruction; *Special Senses:* Tinnitus, dry eyes; *Urogenital:* Urination difficulties.

Potential Adverse Effects: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents and may be considered potential effects of ophthalmic timolol maleate: *Digestive:* Mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Agranulocytosis, thrombocytopenic purpura; *Nervous System:* Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Urogenital:* Peyronie's disease.

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis sicca, otitis, and sclerosing serositis attributed to the beta-adrenergic receptor blocking agent practolol. This syndrome has not been reported with timolol maleate.

HOW SUPPLIED: TIMOPTIC Ophthalmic Solution, 0.25% and TIMOPTIC Ophthalmic Solution, 0.5%. Both are available in 2.5-mL, 5-mL, 10-mL, and 15-mL plastic OCUMETER® ophthalmic dispensers with a controlled drop tip. **Also Available:** Preservative-free TIMOPTIC in OCUDOSE® (Dispenser) Sterile Ophthalmic Unit-Dose Dispenser (see separate Prescribing Information).

Storage: Protect from light. Store at room temperature.

*The maximum recommended single oral dose is 30 mg of timolol. One drop of TIMOPTIC 0.5% contains about 1/150 of this dose, which is about 0.2 mg.

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*L.T. Jones M.D., Dacryocystorhinostomy, American Journal of Ophthalmology, Volume 59, No. 5, May, 1965.

J.C. Mustarde', L.T. Jones M.D. and A. Callahan M.D., Ophthalmic Plastic Surgery---Up-To-Date, Aesculapius Publishing Company, 1970.

L.T. Jones M.D. and J.L. Wobig M.D., Surgery of the Eyelids and Lacrimal System, Aesculapius Publishing Company, 1976.

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Irregular Pupil Cycling as a Characteristic Abnormality in Patients With Demyelinative Optic Neuropathy

John G. Milton, M.D., André Longtin, M.Sc., Trevor H. Kirkham, M.D., and Gordon S. Francis, M.D.

We used an infrared videopupillometer combined with an electronic circuit that regulated the retinal light level as a function of pupil area to assess the regularity of pupil cycling in normal subjects and in patients with known abnormalities in the pupil light reflex pathways. The light stimulus was turned on whenever pupil area exceeded a preset value. Two types of abnormalities were observed for patients with demyelinative optic neuropathy: a failure of the pupil to cycle despite a preserved pupillary response to a single light pulse; and, for those patients in whom cycling was possible, a characteristic intermittent irregularity in the amplitude of pupil cycling. These abnormalities were not seen in normal subjects or in patients with ischemic optic neuropathy, surgical lesions involving the optic chiasm, Adie's syndrome, or Horner's syndrome.

© American Journal of Ophthalmology 105:402–407, April, 1988

Effects of Yellow Filter Glasses on the Results of Photopic and Scotopic Photometry

Eero A. Aarnisalo, M.D.

I measured the luminosity of a white surface with seven different yellow filter glasses and a photometer with two different sensitivities, which resembled the photopic and scotopic sensitivity of a Commision Internationale d'Eclairage standard observer. When measured with filters GG 400, GG 420, GG 435, and GG 455, there was a small and almost equal reduction in the relative photopic and scotopic luminosities. Measured with filters GG 475, GG 495, and OG 515, there was a more marked reduction in the scotopic luminosities than in the photopic luminosities.

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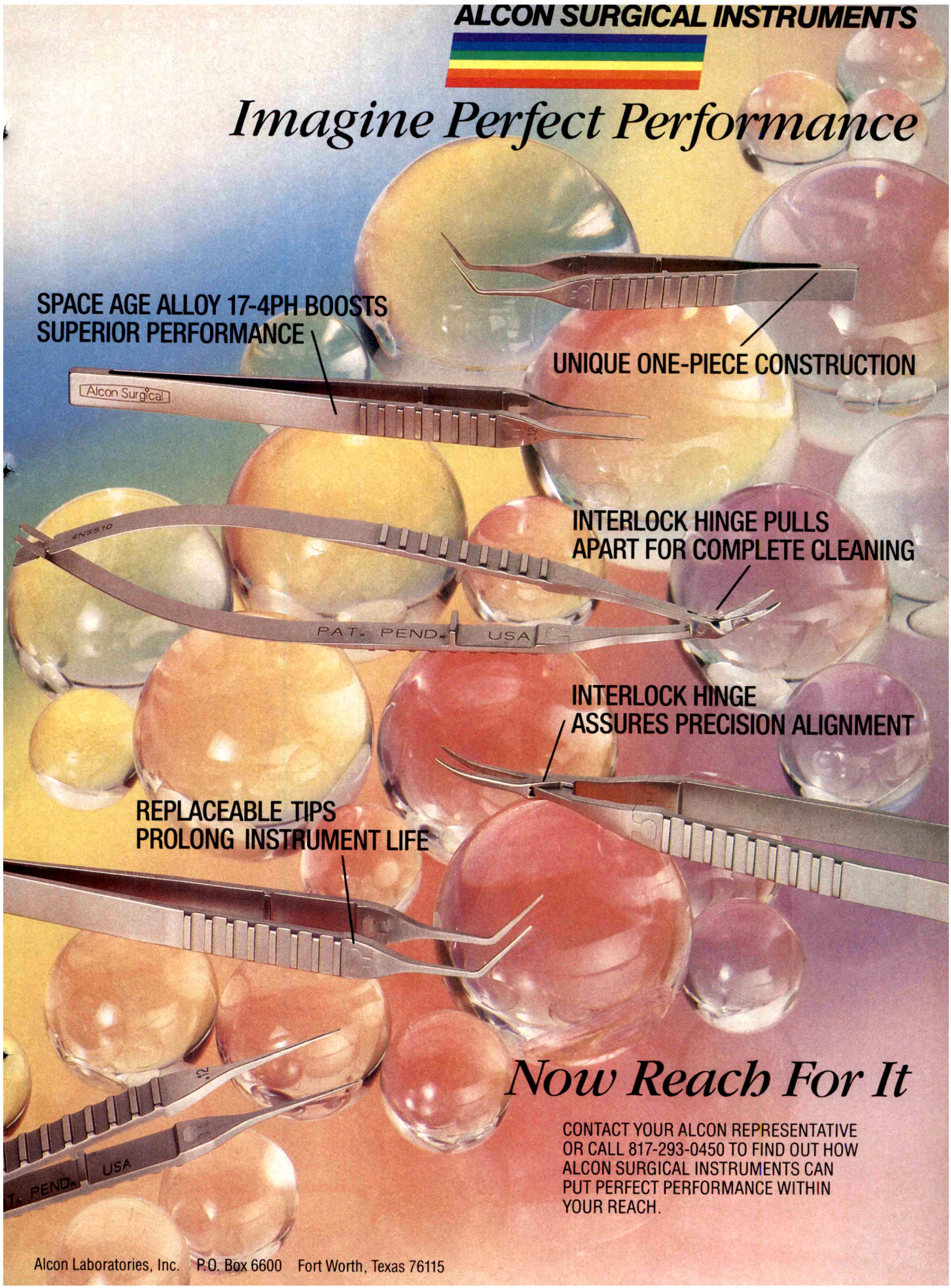
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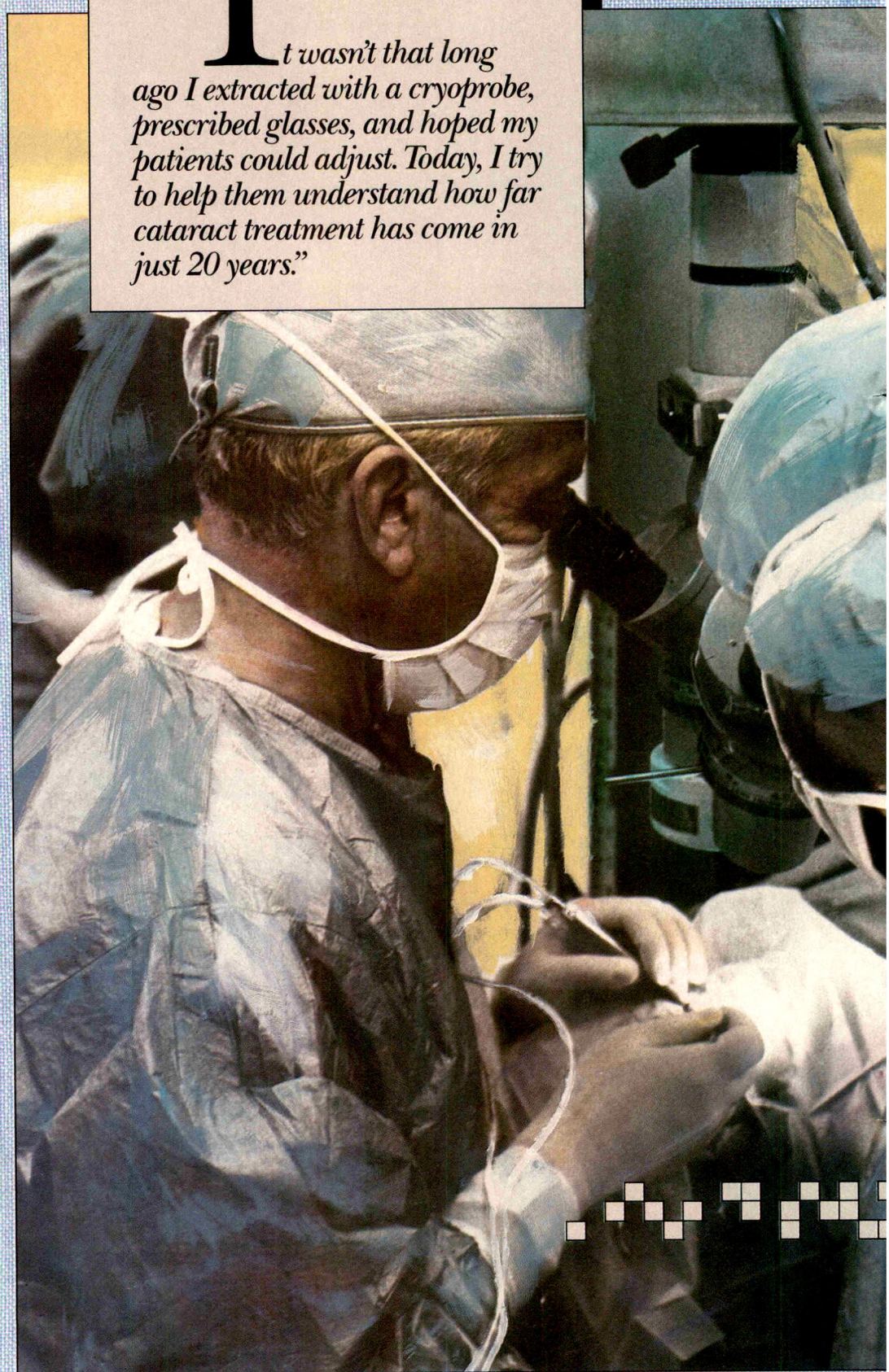
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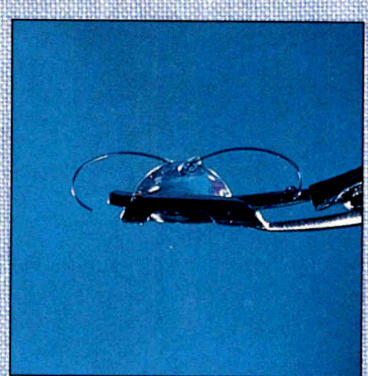
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Please see adjacent page for brief summary of prescribing information.

Ocufen®
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Liquifilm® sterile ophthalmic solution

INDICATIONS AND USAGE
Ocufen is indicated for the inhibition of intraoperative miosis.

CONTRAINDICATIONS
Ocufen is contraindicated in epithelial herpes simplex keratitis (dendritic keratitis) and in individuals who are hypersensitive to any components of the medication.

WARNINGS
There exists the potential for cross-sensitivity to acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

PRECAUTIONS
General: Patients with histories of herpes simplex keratitis should be monitored closely. Ocufen is contraindicated in patients with active herpes simplex keratitis. Wound healing may be delayed with the use of Ocufen.

Drug interactions: Interaction of Ocufen® (flurbiprofen sodium) 0.03% Liquifilm® sterile ophthalmic solution with other topical ophthalmic medications has not been fully investigated.

Although clinical studies with acetylcholine chloride and animal studies with acetylcholine chloride or carbachol revealed no interference, and there is no known pharmacological basis for an interaction, there have been reports that acetylcholine chloride and carbachol have been ineffective when used in patients treated with Ocufen.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term studies in mice and/or rats have shown no evidence of carcinogenicity or impairment of fertility with flurbiprofen. Long-term mutagenicity studies in animals have not been performed.

Pregnancy: Pregnancy category C. Flurbiprofen has been shown to be embryocidal, delay parturition, prolong gestation, reduce weight, and/or slightly retard growth of fetuses when given to rats in daily oral doses of 0.4 mg/kg (approximately 185 times the human daily topical dose) and above. There are no adequate and well-controlled studies in pregnant women. Ocufen should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from flurbiprofen sodium, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
The most frequent adverse reactions reported with the use of Ocufen are transient burning and stinging upon instillation and other minor symptoms of ocular irritation.

It is known that some systemic absorption does occur with ocularly applied drugs, and that nonsteroidal anti-inflammatory drugs have been shown to increase bleeding time by interference with thrombocyte aggregation. There have been reports that ocularly applied Ocufen may cause an increased bleeding tendency of ocular tissues in conjunction with surgery. It is recommended that Ocufen be used with caution in surgical patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

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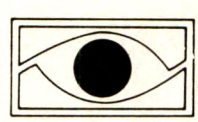
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Summary of Product Information

USES

Healon® is indicated for use as a surgical aid in cataract extraction (intra- and extracapsular), IOL implantation, corneal transplant, glaucoma filtration and retinal attachment surgery.

In surgical procedures in the anterior segment of the eye, instillation of Healon® serves to maintain a deep anterior chamber during surgery, allowing for efficient manipulation with less trauma to the corneal endothelium and other surrounding tissues.

Furthermore, its viscoelasticity helps to push back the vitreous face and prevent formation of a postoperative flat chamber.

In posterior segment surgery Healon® serves as a surgical aid to gently separate, maneuver and hold tissues. Healon® creates a clear field of vision thereby facilitating intra- and postoperative inspection of the retina and photocoagulation.

CONTRAINDICATIONS

At present there are no known contraindications to the use of Healon® when used as recommended.

PRECAUTIONS

Those normally associated with the surgical procedure being performed.

Overfilling the anterior or posterior segment of the eye with Healon® may cause increased intraocular pressure, glaucoma, or other ocular damage.

Postoperative intraocular pressure may also be elevated as a result of pre-existing glaucoma, compromised outflow, and by operative procedures and sequelae thereto, including enzymatic zonulysis, absence of an iridectomy, trauma to filtration structures, and by blood and lenticular remnants in the anterior chamber. Since the exact role of these factors is difficult to predict in any individual case, the following precautions are recommended:

- Don't overfill the eye chambers with Healon® (except in glaucoma surgery—see Application section).
- In posterior segment procedures in aphakic diabetic patients special care should be exercised to avoid using large amounts of Healon®
- Remove some of the Healon® by irrigation and/or aspiration at the close of surgery (except in glaucoma surgery—see Application section).
- Carefully monitor intraocular pressure, especially during the immediate postoperative period. If significant rises are observed, treat with appropriate therapy.

Care should be taken to avoid trapping air bubbles behind Healon®

Because Healon® is a highly purified fraction extracted from avian tissues and is known to contain minute amounts of protein, the physician should be aware of potential risks of the type that can occur with the injection of any biological material.

Because of reports of an occasional release of minute rubber particles, presumably formed when the diaphragm is punctured, the physician should be aware of this potential problem. Express a small amount of Healon® from the syringe prior to use, and carefully examine the remainder as it is injected.

Avoid reuse of cannulas. If reuse becomes necessary, rinse cannula thoroughly with sterile distilled water.

Sporadic reports have been received indicating that Healon® may become "cloudy" or form a slight precipitate following instillation into the eye. The clinical significance of these reports, if any, is not known since the majority received to date do not indicate any harmful effects on ocular tissues. The physician should be aware of this phenomenon and, should it be observed, remove the cloudy or precipitated material by irrigation and/or aspiration.

In vitro laboratory studies suggest that this phenomenon may be related to interactions with certain concomitantly administered ophthalmic medications.

Use only if solution is clear.

ADVERSE REACTIONS

Healon® is extremely well tolerated after injection into human eyes. A transient rise of intraocular pressure postoperatively has been reported in some cases.

In posterior segment surgery intraocular pressure rises have been reported in some patients, especially in aphakic diabetics, after injection of large amounts of Healon®

Rarely, postoperative inflammatory reactions (iritis, hypopyon) as well as incidents of corneal edema and corneal decompensation have been reported. Their relationship to Healon® has not been established.

HOW SUPPLIED

Healon® is a sterile, nonpyrogenic, viscoelastic preparation supplied in disposable glass syringes, delivering 2.0 ml, 0.75 ml, 0.55 ml or 0.4 ml sodium hyaluronate (10 mg/ml) dissolved in physiological sodium chloride-phosphate buffer (pH 7.0-7.5). Each ml of Healon® contains 10 mg of sodium hyaluronate, 8.5 mg of sodium chloride, 0.28 mg of disodium hydrogen phosphate dihydrate, 0.04 mg of sodium dihydrogen phosphate hydrate and q.s. water for injection U.S.P. Healon® syringes are terminally sterilized and aseptically packaged. A sterile single-use, 27-gauge cannula is enclosed in the 0.4-ml, 0.55-ml, and 0.75-ml boxes.

Refrigerated Healon® should be allowed to attain room temperature (approximately 30 minutes) prior to use.

For intraocular use.
Store at 2—8°C.
Protect from freezing.
Protect from light.

CAUTION

Federal law restricts this device to sale by or on the order of a physician.

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Uppsala, Sweden

For: Pharmacia Ophthalmics, Inc
Pasadena, CA 91107

Revised: January 1988
Healon is covered by
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MEETINGS

UPDATE ON DIABETIC RETINOPATHY

Friday, May 20, 1988
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George Blankenship, M.D.
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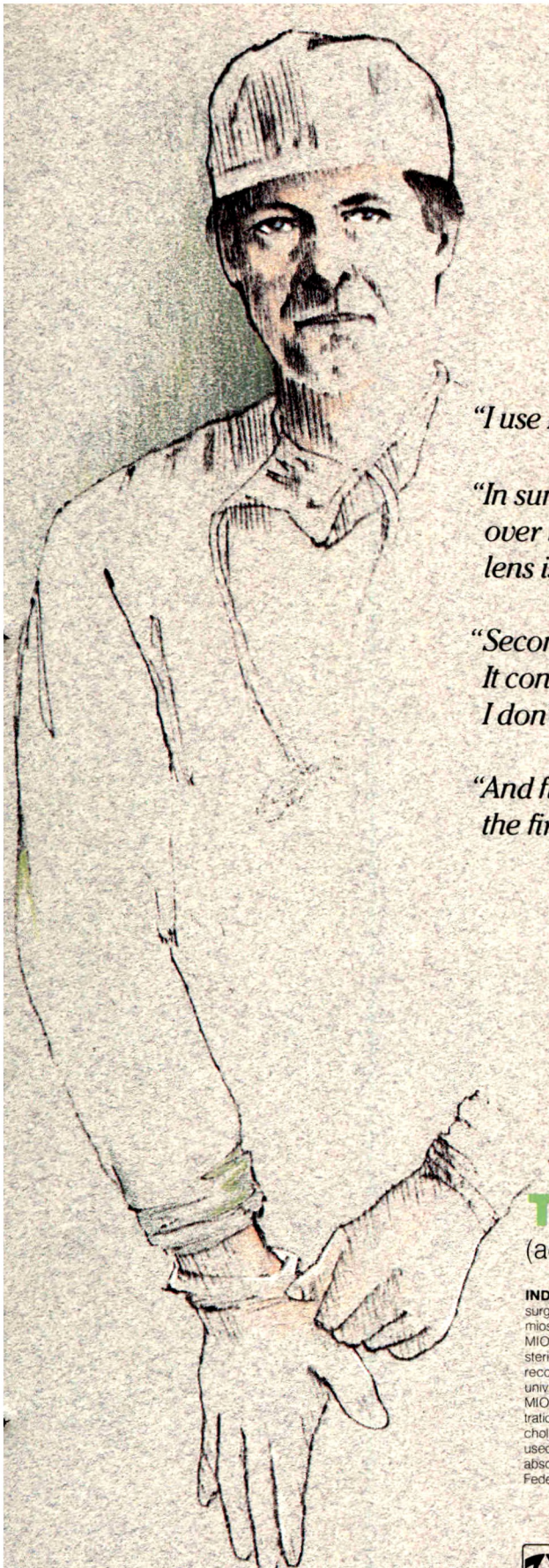
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Robt Maynor M.D.

October 5, 1987. Huntsville, AL

Dr. Maynor was not reimbursed for these comments about his use of Miochol® in his practice.

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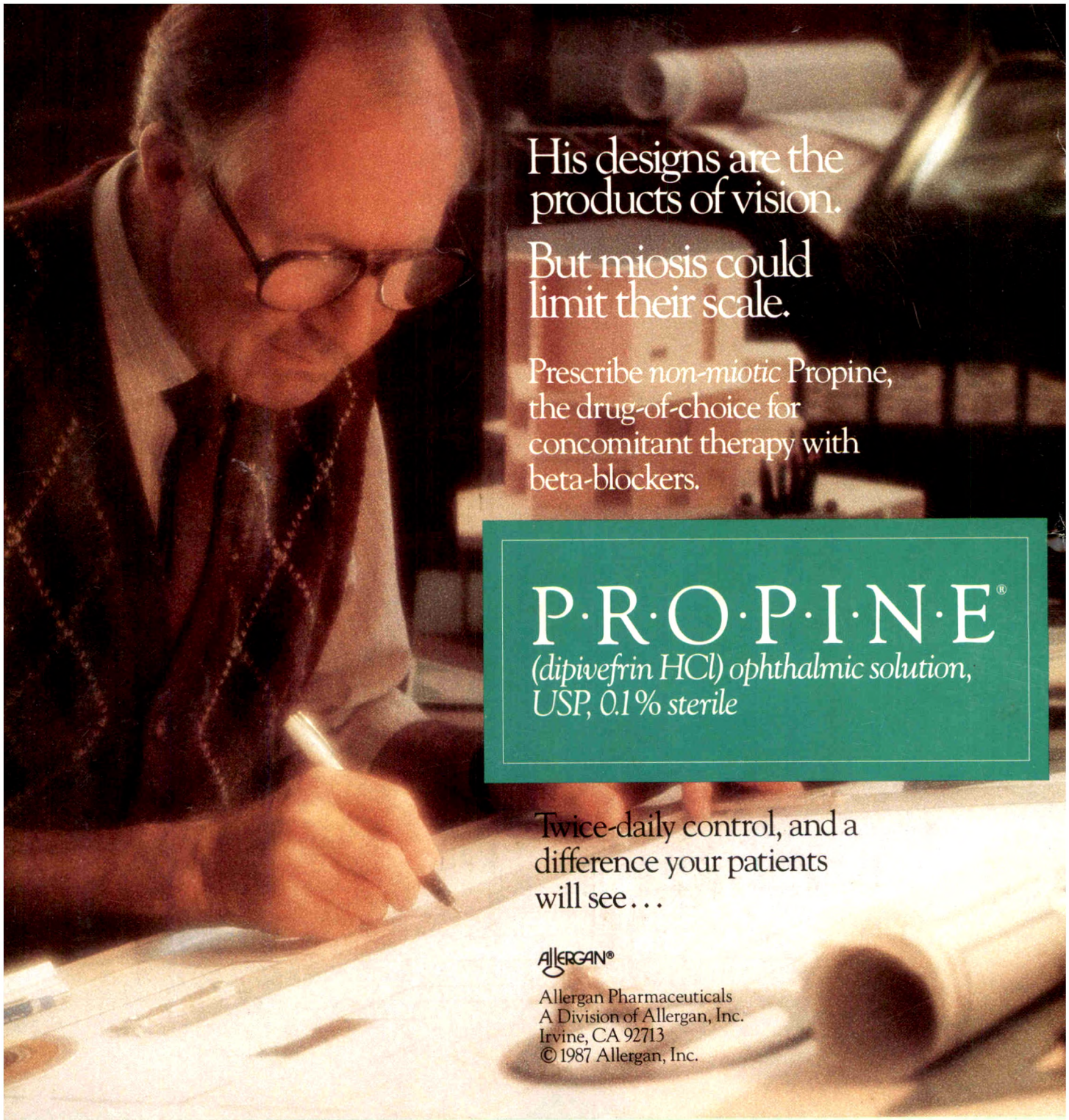
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INDICATIONS: To obtain complete miosis in seconds, by irrigation of the iris after delivery of the lens in cataract surgery, as well as penetrating keratoplasty, iridectomy and other anterior segment surgery where rapid, complete miosis may be required. **CONTRAINDICATIONS:** There are presently no known contraindications to the use of MIOCHOL (acetylcholine chloride) Intraocular. **WARNINGS:** If blister or paper backing is damaged or broken, sterility of the enclosed bottle cannot be assured. Open under aseptic conditions only. **PRECAUTIONS:** In the reconstitution of the solution, as described under Directions for Using Univial, if the center rubber plug seal in the univial does not go down or is down, do not use the vial. If miosis is to be obtained quickly and completely with MIOCHOL, obstructions to miosis, such as anterior or posterior synechiae, may require surgery prior to administration of MIOCHOL. In cataract surgery, use MIOCHOL only after delivery of the lens. Aqueous solutions of acetylcholine chloride are unstable. Prepare solution immediately before use. Discard any solution that has not been used. **ADVERSE REACTIONS:** Adverse reactions have been reported rarely which are indicative of systemic absorption. These include: bradycardia, hypotension, flushing, breathing difficulties and sweating. **CAUTION:** Federal law prohibits dispensing without prescription. **HOW SUPPLIED:** 2 ml sterile univial. **NDC** 0058-2757-45.

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Propine®
(dipivefrin hydrochloride) ophthalmic solution, USP, 0.1% sterile **INDICATIONS:** Propine (dipivefrin HCl) is indicated as initial therapy for the control of intraocular pressure in chronic open-angle glaucoma. Patients responding inadequately to other antiglaucoma therapy may respond to addition of Propine. In controlled and open label studies of glaucoma, Propine demonstrated a statistically significant intraocular pressure-lowering effect. Patients using Propine twice daily in studies with mean durations of 76-146 days experienced mean pressure reductions ranging from 20-24%. Therapeutic response to Propine twice daily is somewhat less than 2% epinephrine twice daily. Controlled studies showed statistically significant differences in lowering of intraocular pressure between Propine and 2% epinephrine. In controlled studies in patients with a history of epinephrine intolerance, only 3% of patients treated with Propine exhibited intolerance, while 55% of those treated with epinephrine again developed intolerance. Therapeutic response to Propine twice daily therapy is comparable to 2% pilocarpine 4 times daily. In controlled clinical studies comparing Propine and 2% pilocarpine, there were no statistically significant differences in the maintenance of IOP levels for the two medications. Propine does not produce miosis or accommodative spasm which cholinergic agents are known to produce. The blurred vision and night blindness often associated with miotic agents are not present with Propine therapy. Patients with cataracts avoid the inability to see around lenticular opacities caused by constricted pupil. **CONTRAINDICATIONS:** Propine® should not be used in patients with narrow angles since any dilation of the pupil may predispose the patient to an attack of angle-closure glaucoma. This product is contraindicated in patients who are hypersensitive to any of its components. **PRECAUTIONS: Aphakic Patients.** Macular edema has been shown to occur in up to 30% of aphakic patients treated with epinephrine. Discontinuation of epinephrine generally results in reversal of the maculopathy. **Pregnancy Category B.** Reproduction studies have been performed in rats and rabbits at daily oral doses up to 10 mg/kg body weight (5 mg/kg in teratogenicity studies), and have revealed no evidence of impaired fertility or harm to the fetus due to dipivefrin HCl. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Nursing Mothers.** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Propine is administered to a nursing woman. **Usage in Children.** Clinical studies for safety and efficacy in children have not been done. **Animal Studies.** Rabbit studies indicated a dose-related incidence of meibomian gland retention cysts following topical administration of both dipivefrin hydrochloride and epinephrine. **ADVERSE REACTIONS: Cardiovascular Effects.** Tachycardia, arrythmias and hypertension have been reported with ocular administration of epinephrine. **Local Effects.** The most frequent side effects reported with Propine alone were injection at 6.5% and burning and stinging at 6% of patient eye visits. Epinephrine therapy can lead to adrenochrome deposits in the conjunctiva and cornea.

MAY 15

1988

AMERICAN JOURNAL OF OPHTHALMOLOGY

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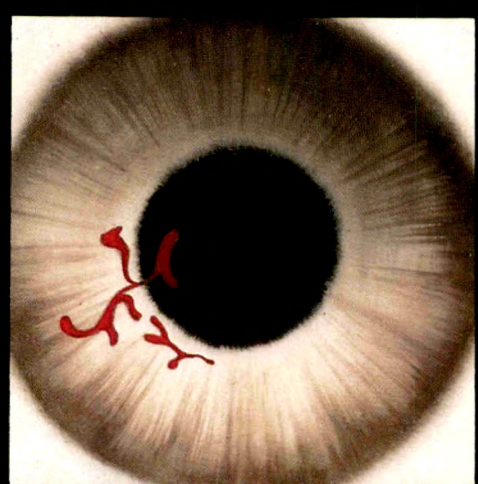
Cartilagenous choristoma of the eyelid tarsus
Mauriello, Voglino, Otazo

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In two different clinical trials comparing Viroptic to IDU (idoxuridine) and ARA-A (adenine arabinoside or vidarabine) in the healing of dendritic lesions, Viroptic demonstrated superior efficacy.[1,2]



(Medical artist's conception of typical Dendritic Lesion)

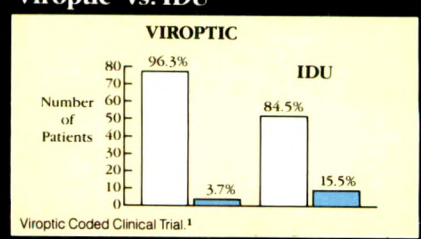
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In two different clinical trials comparing Viroptic to IDU and ARA-A in the healing of geographic lesions, Viroptic again proved to be superior in efficacy.[1,2]



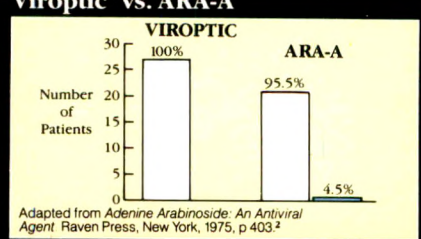
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Viroptic® vs. IDU



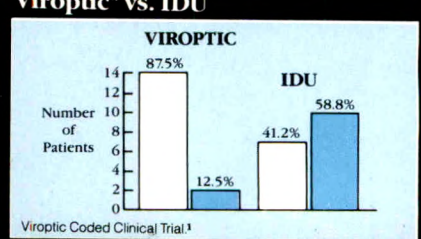
Viroptic Coded Clinical Trial.[1]

Viroptic® vs. ARA-A



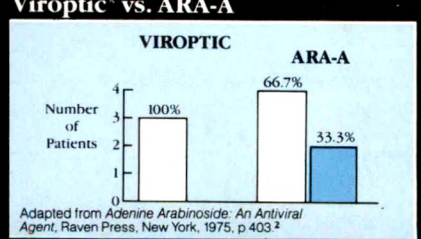
Adapted from *Adenine Arabinoside: An Antiviral Agent* Raven Press, New York, 1975, p 403.[2]

Viroptic® vs. IDU



Viroptic Coded Clinical Trial.[1]

Viroptic® vs. ARA-A



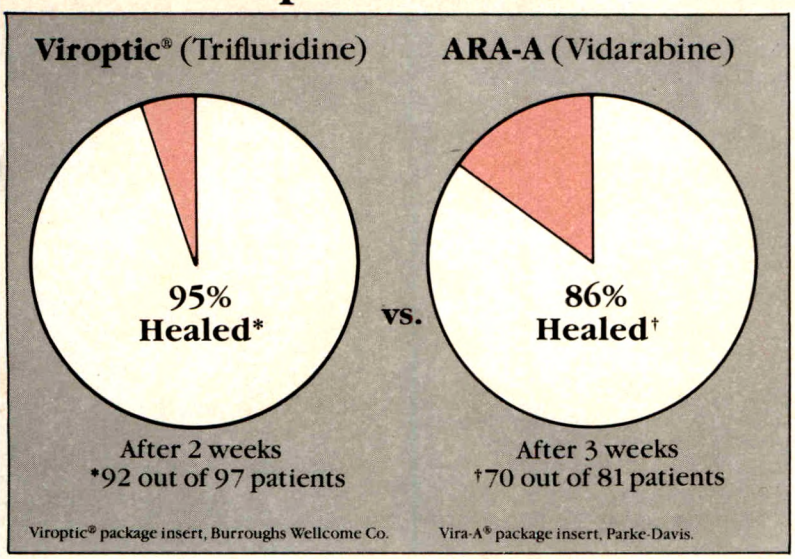
Adapted from *Adenine Arabinoside: An Antiviral Agent*, Raven Press, New York, 1975, p 403.[2]

Number of Patients Healed

Number of Patients Not Healed

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Viroptic® vs ARA-A



Ninety-five percent of patients in Viroptic clinical trials responded within two weeks. By contrast, an examination of controlled trials for ARA-A (vidarabine) reveals that 86% of patients had responded (corneal re-epithelialization had occurred) after three weeks of therapy. So for some patients, treatment with Viroptic may mean relief from suffering and recovery from herpetic keratitis a full week sooner.

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"We do use idoxuridine and vidarabine where acute infections do not respond to trifluridine, but, in my opinion, trifluridine is now the drug of choice for the treatment of superficial herpes, with no exceptions."[3]

References

1. Data on file, Medical Division, Burroughs Wellcome Co.
2. McKinnon JR, McGill JI, Jones BR: A coded clinical evaluation of adenine arabinoside and trifluorothymidine in the treatment of ulcerative herpetic keratitis, in Pavan-Langston D, Buchanan RA, Alford CA Jr (eds): *Adenine Arabinoside: An Antiviral Agent,* Raven Press, New York, 1975, p 403.
3. Kaufman HE, Centifanto-Fitzgerald YM, Varnell ED: Herpes simplex keratitis. *Ophthalmology* 1983;90:700-706.

A First Choice for treating Epithelial Keratitis caused by Herpes Simplex Virus

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CONTRAINDICATIONS: Hypersensitivity or chemical intolerance to trifluridine.

WARNINGS: Do not administer more than nine drops daily. If there is no sign of improvement after seven days or complete re-epithelialization has not occurred after 14 days, other forms of therapy should be considered. Avoid administering VIROPTIC continuously for longer than 21 days.

PRECAUTIONS:

General: Prescribe only for clinically diagnosed herpetic keratitis. May cause mild local irritation (usually transient). Viral resistance may possibly develop, though it has not been reported *in vitro.*

Drug Interactions: VIROPTIC has been administered without apparent adverse interaction with certain antibiotics, certain steroids, and certain other ophthalmic drugs. Please see complete prescribing information.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies of mutagenicity and oncogenicity have been inconclusive.

Pregnancy: Do not use in pregnant women unless potential benefits outweigh potential risks. Based upon animal findings, it is unlikely that VIROPTIC would cause embryonic or fetal damage if given in recommended ophthalmic dosage to pregnant women. A safe dose has not been established for human embryo or fetus.

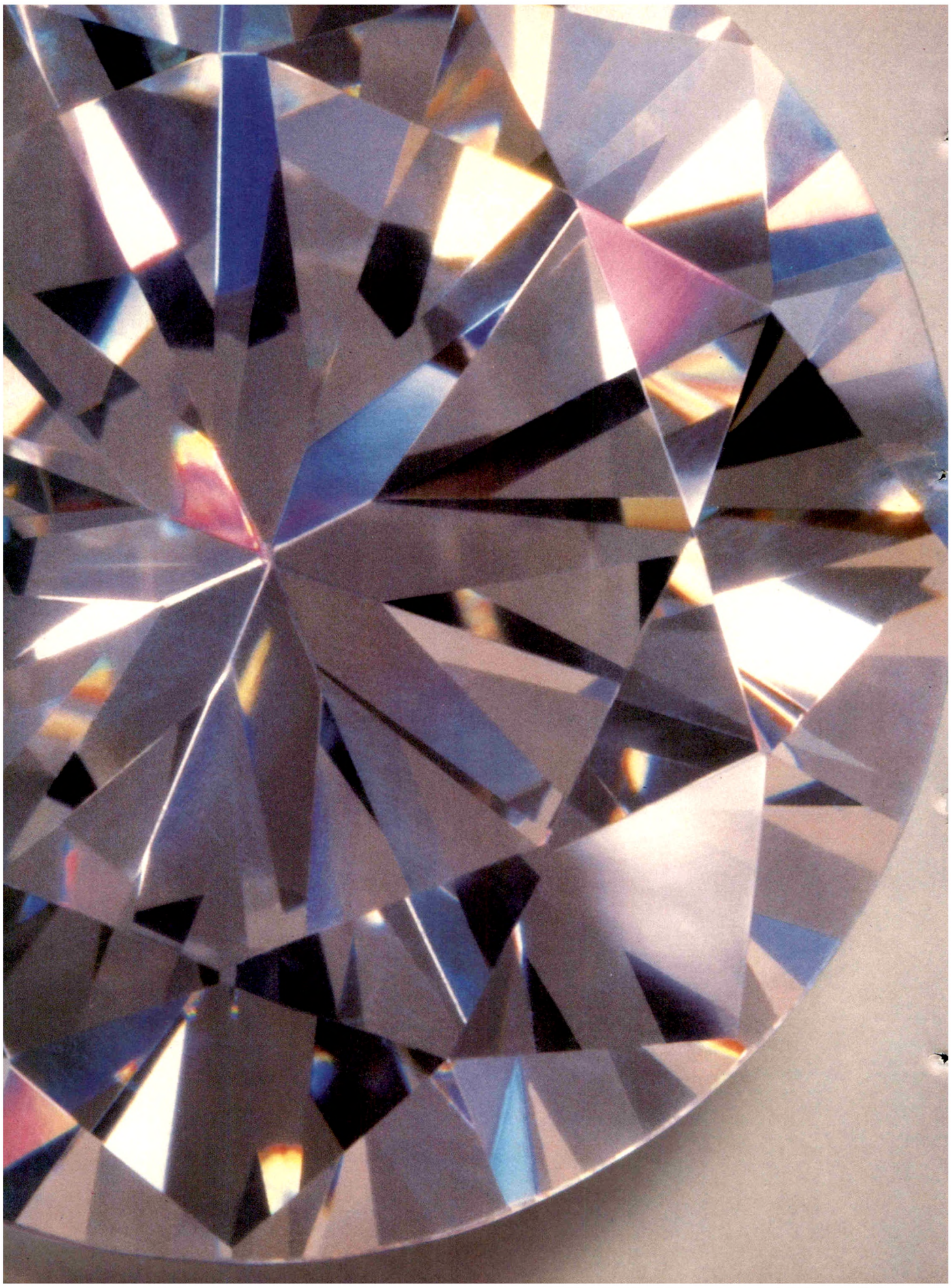
Nursing Mothers: It is unlikely that VIROPTIC, administered in the eye as indicated, will be excreted in human milk, but the drug should not be prescribed for nursing mothers unless potential benefits outweigh potential risks.

ADVERSE REACTIONS: Most frequently reported: mild, transient burning or stinging upon instillation (4.6%), palpebral edema (2.8%). Others, in decreasing order of frequency: superficial punctate keratopathy, epithelial keratopathy, hypersensitivity reaction, stromal edema, irritation, keratitis sicca, hyperemia, increased intraocular pressure.

SUPPLIED: 7.5 ml Drop Dose® plastic dispenser bottle.

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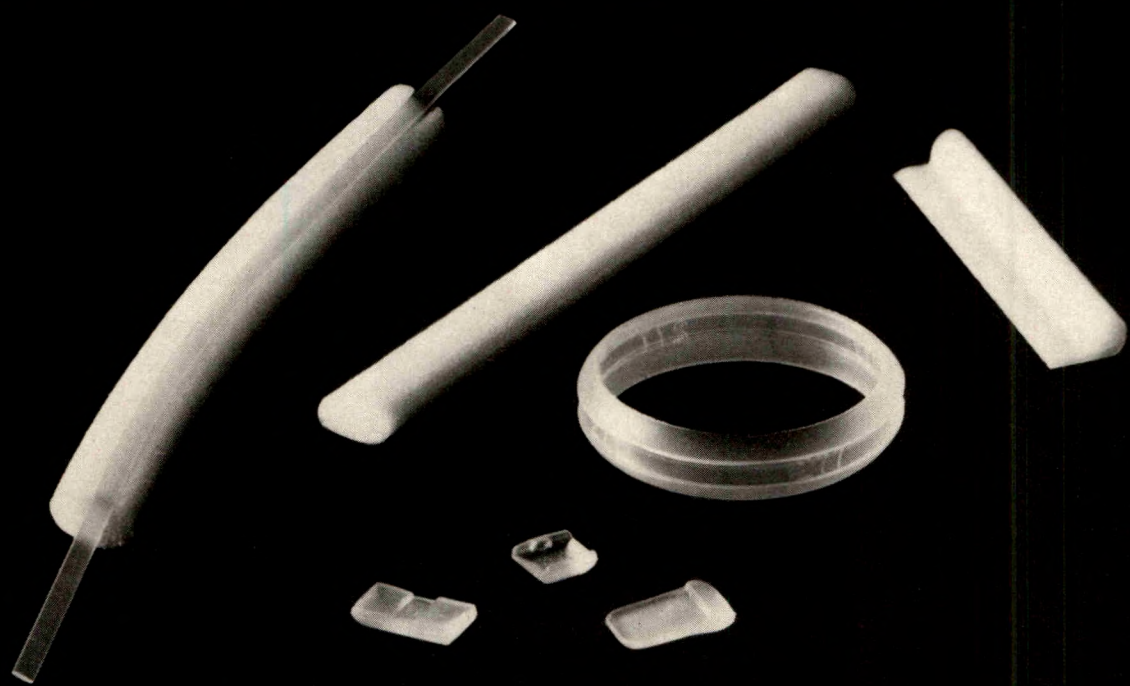
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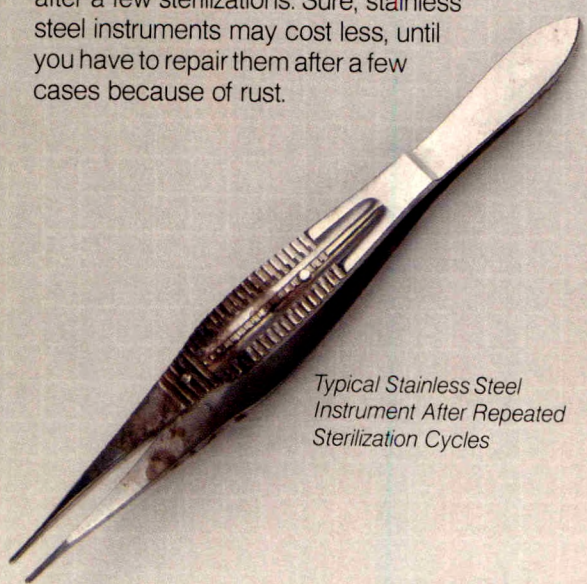
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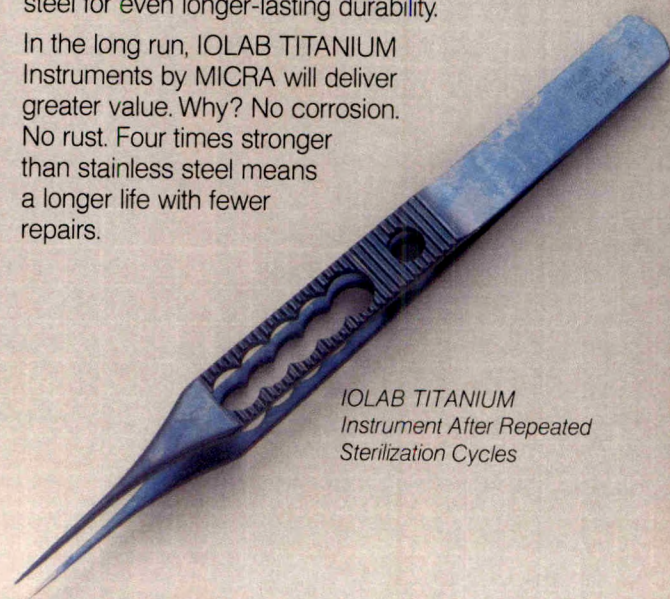


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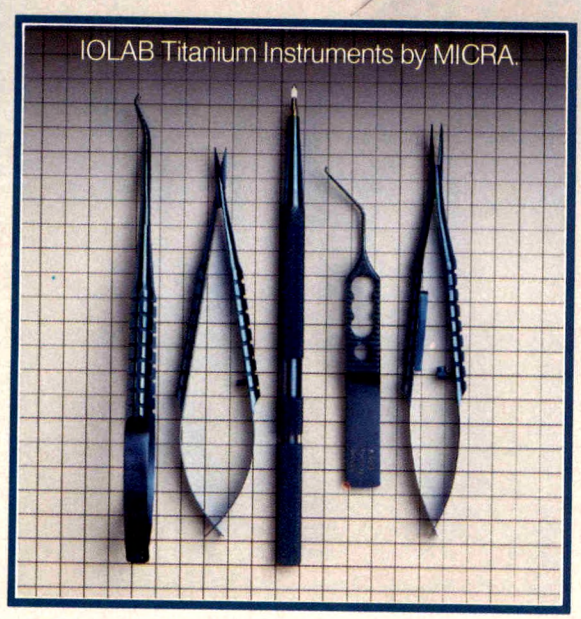
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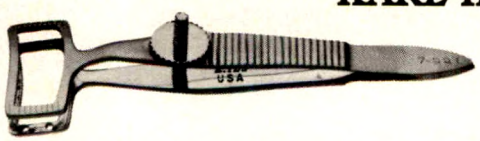
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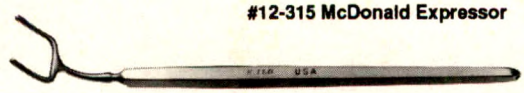
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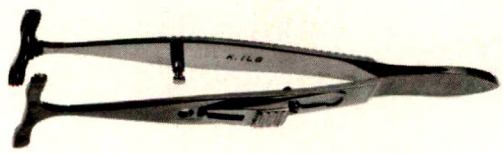
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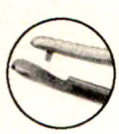
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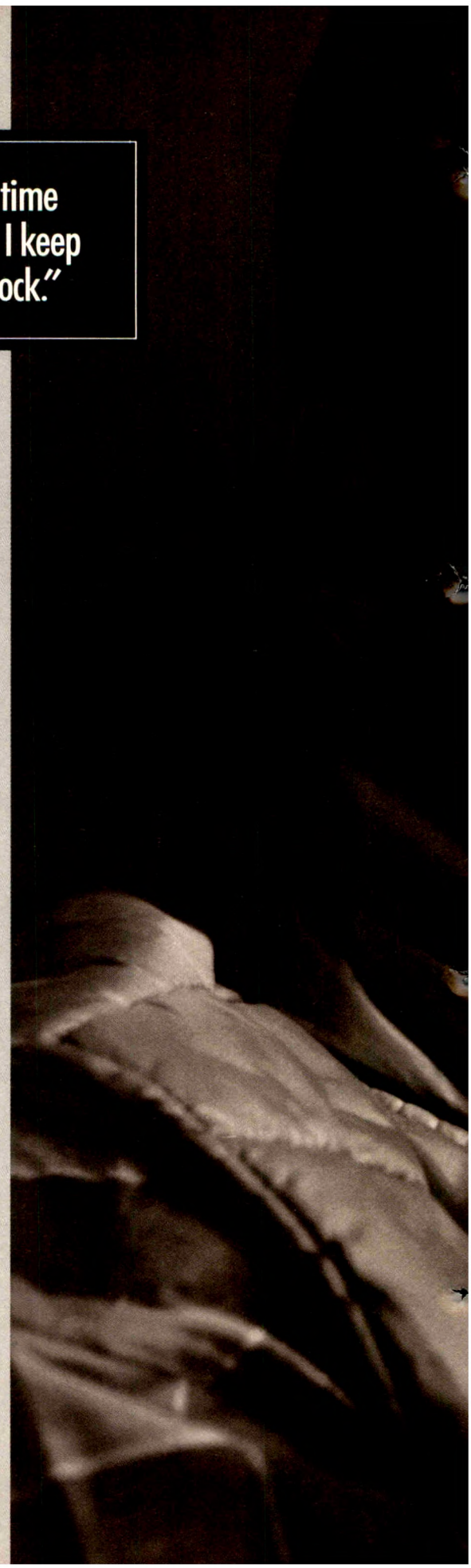
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1. Wandel T. Charap A. Lewis RA et al, Glaucoma treatment with once-daily levobunolol. Am J. Ophthalmol 1986;101:298
2. David R. Ober M. Foerster Ret al. The efficacy of once-daily beta-blockers for glaucoma treatment. Am J. Ophthalmol 1987;104:443
3. Levobunolol Clinical Study Group. Levobunolol: A beta-adrenoceptor antagonist effective in the long-term treatment of glaucoma. Ophthalmology 1985;92:1271.

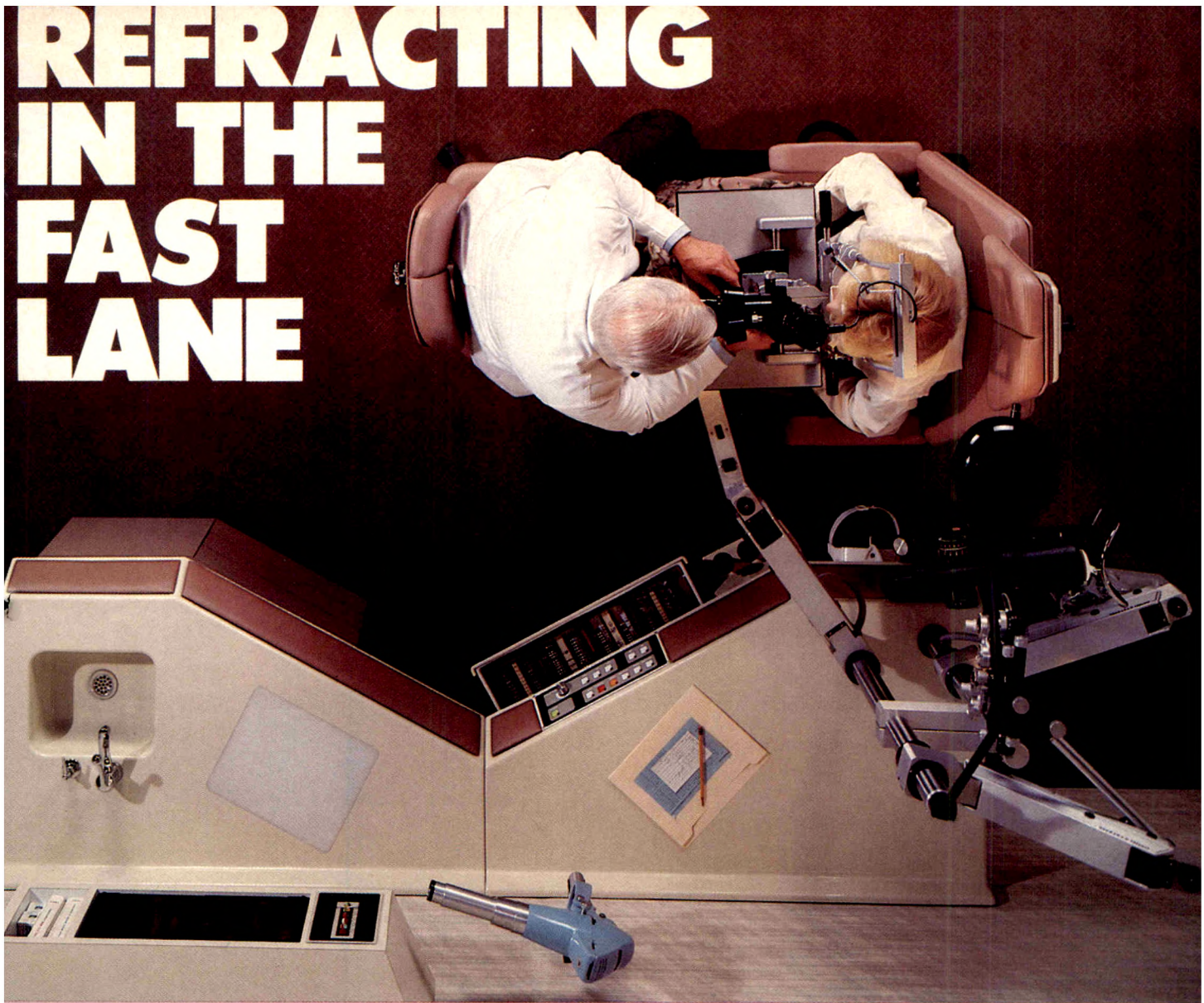
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For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported with topical application of beta-adrenergic blocking agents (see CONTRAINDICATIONS). *Cardiac Failure:* Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. *In Patients Without a History of Cardiac Failure:* Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, BETAGAN should be discontinued. *Non-allergic Bronchospasm:* In patients with non-allergic bronchospasm or with a history of non-allergic bronchospasm (e.g., chronic bronchitis, emphysema), BETAGAN should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of $beta_2$ receptors. *Major Surgery:* The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. For these reasons, in patients undergoing elective surgery, gradual withdrawal of beta-adrenergic receptor blocking agents may be appropriate. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol (see OVERDOSAGE). *Diabetes Mellitus:* Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia. *Thyrotoxicosis:* Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm. Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people. **PRECAUTIONS:** ***General:*** **BETAGAN®** (levobunolol HCl) 0.5% Liquifilm® sterile ophthalmic solution should be used with caution in patients with known hypersensitivity to other beta-adrenoceptor blocking agents. Use with caution in patients with known diminished pulmonary function. In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. BETAGAN has little or no effect on the pupil. When BETAGAN is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone. *Muscle Weakness:* Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalized weakness). *Drug Interactions:* BETAGAN should be used with caution in patients who are receiving a beta-adrenergic blocking agent orally, because of the potential for additive effects on systemic beta-blockade. Although BETAGAN used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with BETAGAN and epinephrine may occur. Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension. *Animal Studies:* No adverse ocular effects were observed in rabbits administered BETAGAN topically in studies lasting one year in concentrations up to 10 times the human dose concentration. *Carcinogenesis, mutagenesis, impairment of fertility:* In a lifetime oral study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign leiomyomas in female mice at 200 mg/kg/day (14,000 times the recommended human dose for glaucoma), but not at 12 or 50 mg/ kg/day (850 and 3,500 times the human dose). In a two-year oral study of levobunolol HCl in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of benign hepatomas in male rats administered 12,800 times the recommended human dose for glaucoma. Similar differences were not observed in rats administered oral doses equivalent to 350 times to 2,000 times the recommended human dose for glaucoma. Levobunolol did not show evidence of mutagenic activity in a battery of microbiological and mammalian *in vitro* and *in vivo* assays. Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 1,800 times the recommended human dose for glaucoma. *Pregnancy Category C:* Fetotoxicity (as evidenced by a greater number of resorption sites) has been observed in rabbits when doses of levobunolol HCl equivalent to 200 and 700 times the recommended dose for the treatment of glaucoma were given. No fetotoxic effects have been observed in similar studies with rats at up to 1,800 times the human dose for glaucoma. Teratogenic studies with levobunolol in rats at doses up to 25 mg/kg/day (1,800 times the recommended human dose for glaucoma) showed no evidence of fetal malformations. There were no adverse effects on postnatal development of offspring. It appears when results from studies using rats and studies with other beta-adrenergic blockers are examined, that the rabbit may be a particularly sensitive species. There are no adequate and well-controlled studies in pregnant women. BETAGAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Nursing Mothers:* It is not known whether this drug is excreted in human milk. Systemic beta-blockers and topical timolol maleate are known to be excreted in human milk. Caution should be exercised when BETAGAN is administered to a nursing woman. *Pediatric Use:* Safety and effectiveness in children have not been established. **ADVERSE REACTIONS:** In clinical trials the use of BETAGAN has been associated with transient ocular burning and stinging in about one in four patients, and with blepharoconjunctivitis in about one in 20 patients. Decreases in heart rate and blood pressure have been reported occasionally (see CONTRAINDICATIONS and WARNINGS). The following adverse effects have been reported rarely with the use of BETAGAN: Iridocyclitis, headache, transient ataxia, dizziness, lethargy, urticaria and pruritus. Decreased corneal sensitivity has been noted in a small number of patients. Although levobunolol has minimal membrane-stabilizing activity, there remains a possibility of decreased corneal sensitivity after prolonged use. The following additional adverse reactions have been reported with ophthalmic use of $beta_1$ and $beta_2$ (non-selective) adrenergic receptor blocking agents: BODY AS A WHOLE: Headache. CARDIOVASCULAR; Arrhythmia, syncope, heart block, cerebral vascular accident, cerebral ischemia, congestive heart failure, palpitation. DIGESTIVE: Nausea. PSYCHIATRIC: Depression. SKIN: Hypersensitivity, including localized and generalized rash. RESPIRATORY: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure. ENDOCRINE: Masked symptoms of hypoglycemia in insulin-dependent diabetics (see WARNINGS). SPECIAL SENSES: Signs and symptoms of keratitis, blepharoptosis, visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis. Other reactions associated with the oral use of non-selective adrenergic receptor blocking agents should be considered potential effects with ophthalmic use of these agents.

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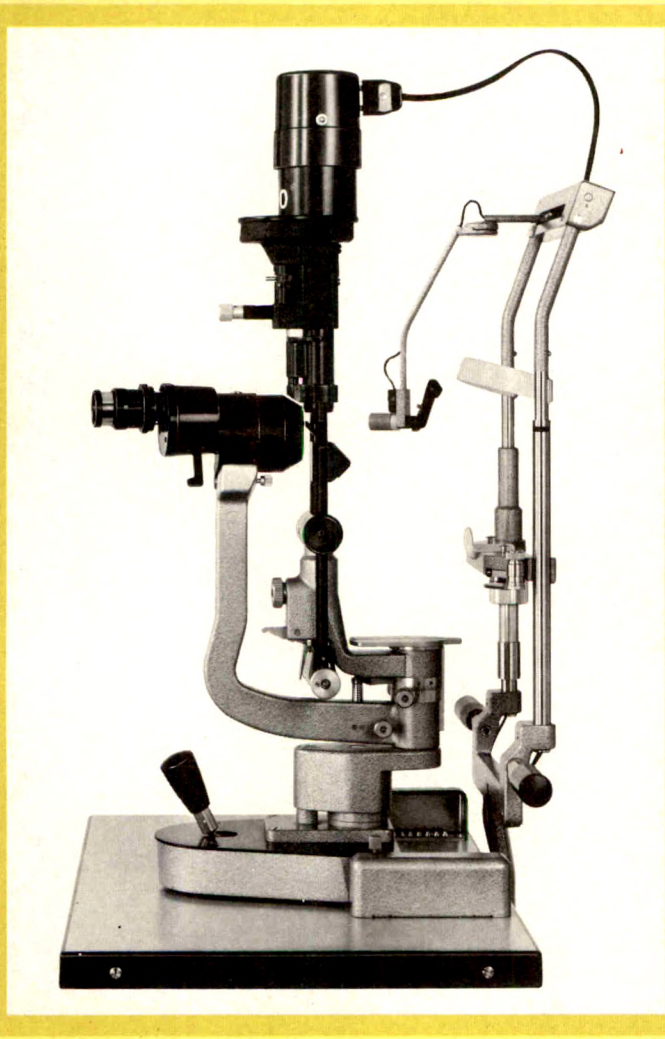
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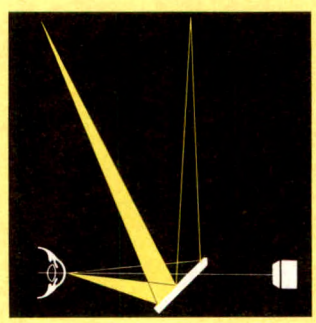
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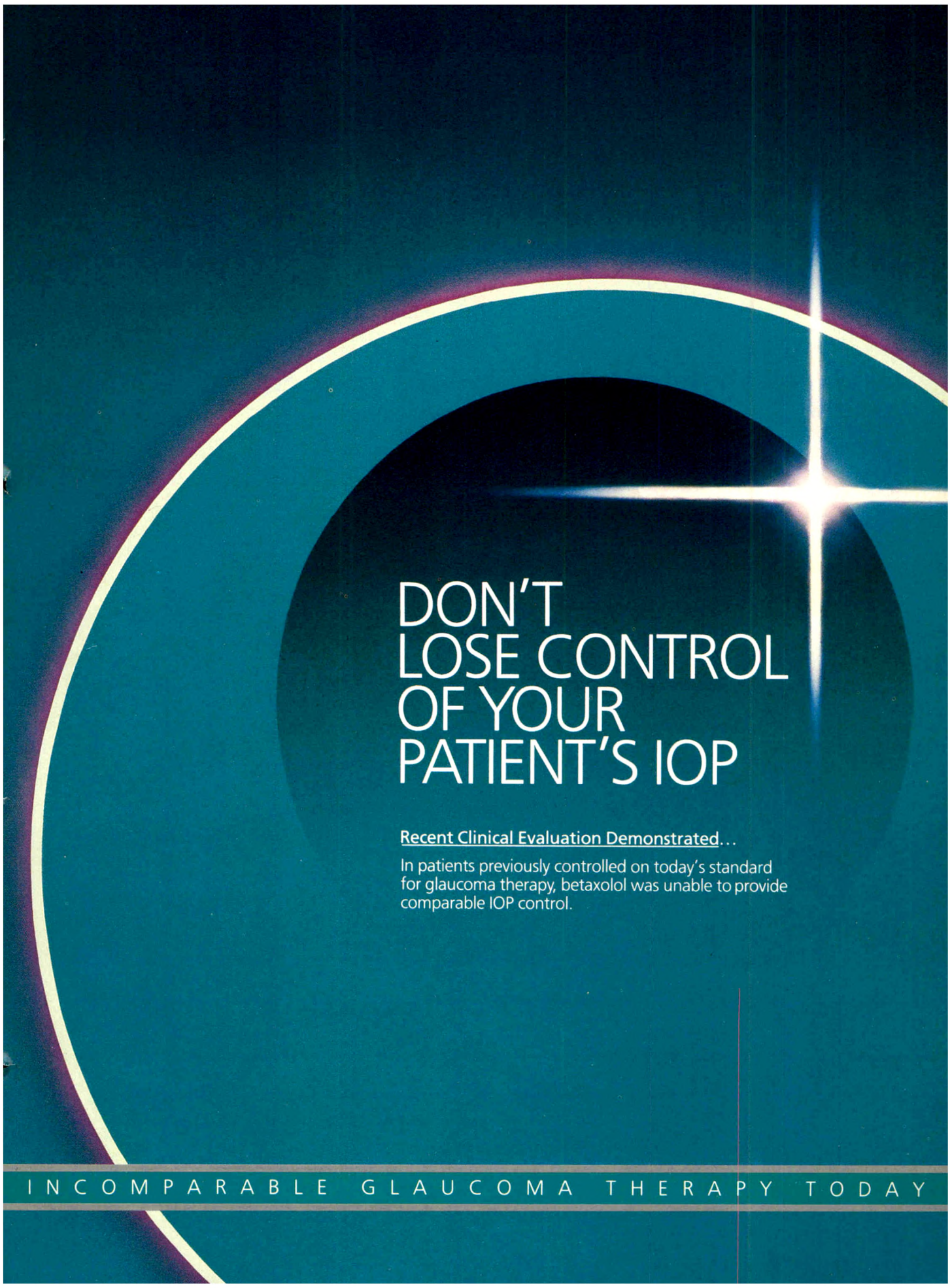
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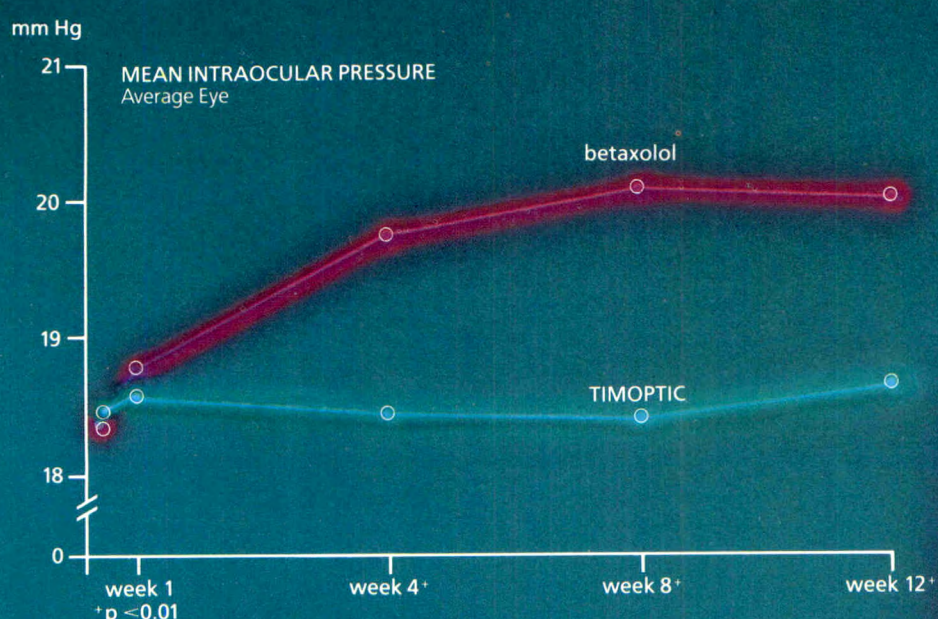

DON'T
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OF YOUR
PATIENT'S IOP
Recent Clinical Evaluation Demonstrated...
In patients previously controlled on today's standard for glaucoma therapy, betaxolol was unable to provide comparable IOP control.
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DON'T LOSE CONTROL OF YOUR PATIENT'S IOP

In a multicenter study, recent clinical evaluation,[1,2] of 353 patients with a history of satisfactory IOP control and tolerability while on TIMOPTIC® (Timolol Maleate, MSD):

- Confirmed the benefits of maintaining therapy with TIMOPTIC for IOP control
- Demonstrated that TIMOPTIC surpassed Betoptic in maintaining IOP control

In patients previously controlled on TIMOPTIC, Betoptic was unable to maintain comparable IOP control:



At week 12, 97% of 149 patients on TIMOPTIC continued to be satisfactorily controlled.

At weeks 4, 8, and 12, significant increases in baseline IOP ($p \leq 0.01$) were seen in the patients treated with Betoptic.

[1]Data available upon request from Merck Sharp & Dohme, Professional Services Department, West Point, PA 19486.

[2]A total of 353 patients whose IOP was satisfactorily controlled with TIMOPTIC and in whom the drug was well tolerated were continued on TIMOPTIC 0.5% b.i.d. during a 2-week baseline period. Patients contributing data were then randomly assigned in a double-masked fashion in demographically similar groups to continue to receive either TIMOPTIC 0.5% b.i.d. (n = 149) or Betoptic 0.5% b.i.d. (n = 146). Following a baseline measurement, patients were evaluated for IOP after 1, 4, 8, and 12 weeks of therapy. In the average-eye approach, values from the right and left eye were averaged at each time point to obtain the values used in the analysis. In the worst-eye approach, the eye with the higher baseline IOP was followed throughout the course of the study.

As with the use of other antiglaucoma drugs, diminished responsiveness to TIMOPTIC after prolonged therapy has been reported in some patients. However, in one long-term study in which 96 patients have been followed for at least 3 years, no significant difference in mean IOP has been observed after initial stabilization.

TIMOPTIC is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; and hypersensitivity to any component of this product.

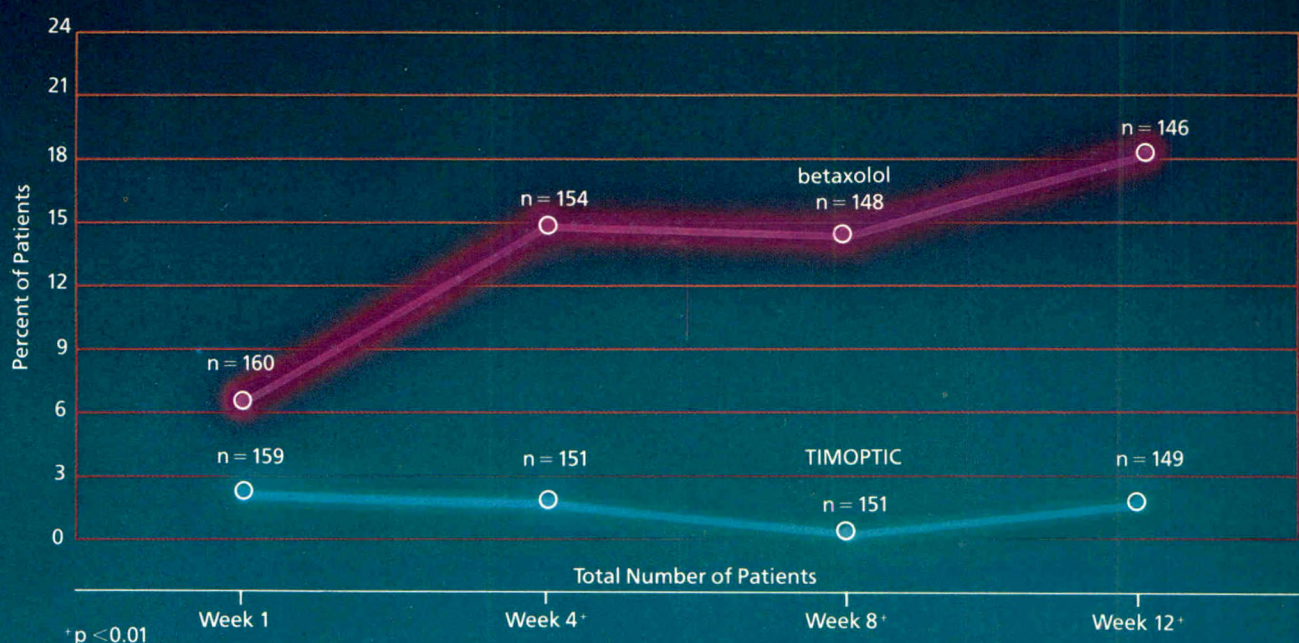
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PATIENTS EXHIBITING CHANGES IN INTRAOCULAR PRESSURE (FROM TREATED BASELINE) ≥ +5 mm Hg

Worst Eye



+p <0.01

Nearly 1 out of 5 patients treated with Betoptic showed an increase in IOP ≥ +5 mm Hg at week 12

For the majority of patients with chronic open-angle glaucoma or elevated IOP who are at sufficient risk to require therapy

TIMOPTIC®

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STERILE OPHTHALMIC SOLUTION

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Before prescribing TIMOPTIC, please see the Brief Summary of Prescribing Information on the following page.

TIMOPTIC®

(TIMOLOL MALEATE) MSD

STERILE OPHTHALMIC SOLUTION

How to start patients on TIMOPTIC:
Usual starting dosage: one drop 0.25% TIMOPTIC in the affected eye(s) twice a day.

How to transfer from another topical ophthalmic beta-adrenergic blocking agent to TIMOPTIC:
1. On the first day, after proper dosing, discontinue the topical agent being used.

2. On the second day, start treatment with one drop of 0.25% TIMOPTIC in the affected eye(s) b.i.d.

How to transfer from a single antiglaucoma agent (other than a topical ophthalmic beta-adrenergic blocking agent) to TIMOPTIC:
1. On the first day, continue with the agent already being used and add one drop 0.25% TIMOPTIC in the affected eye(s) b.i.d.

2. On the second day, discontinue the previously used agent and continue with TIMOPTIC in the affected eye(s) b.i.d.

How to transfer from several concomitantly administered antiglaucoma agents to TIMOPTIC:
1. If any agent is an ophthalmic beta-adrenergic blocker, discontinue before starting TIMOPTIC.

2. Continue the other agents being used, but add one drop of 0.25% TIMOPTIC to the affected eye(s) b.i.d.

3. On the following day, discontinue one of the other antiglaucoma agents.

4. The remaining antiglaucoma agents may be decreased or discontinued according to the patient's response to treatment.

If clinical response is not adequate:
Dosage may be increased (from the 0.25% solution) by changing to one drop 0.5% TIMOPTIC twice a day in the affected eye(s). Dosages above one drop of 0.5% TIMOPTIC twice a day generally have not been shown to produce further reduction of IOP. If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s).

In patients with a history of severe cardiac disease, signs of cardiac failure should be watched for and pulse rates should be checked.

CONTRAINDICATIONS: TIMOPTIC is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to any component of this product.

WARNINGS: As with other topically applied ophthalmic drugs, this drug may be absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death in association with cardiac failure, have been reported following administration of TIMOPTIC (see CONTRAINDICATIONS).

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, TIMOPTIC should be discontinued.

Obstructive Pulmonary Disease: PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (e.g., CHRONIC BRONCHITIS, EMPHYSEMA) OF MILD OR MODERATE SEVERITY, BRONCHOSPASTIC DISEASE OR HISTORY OF BRONCHOSPASTIC DISEASE (OTHER THAN BRONCHIAL ASTHMA OR HISTORY OF BRONCHIAL ASTHMA, IN WHICH 'TIMOPTIC' IS CONTRAINDICATED, see CONTRAINDICATIONS), SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS, INCLUDING 'TIMOPTIC'. However, if TIMOPTIC is necessary in such patients, then the drug should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution to patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

PRECAUTIONS: *General:* Patients who are receiving a beta-adrenergic blocking agent orally and TIMOPTIC should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Patients should not receive two topical ophthalmic beta-adrenergic blocking agents concurrently.

Because of potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with TIMOPTIC, alternative therapy should be considered.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. TIMOPTIC has little or no effect on the pupil. When TIMOPTIC is not alone.

As with the use of other antiglaucoma drugs, diminished responsiveness to TIMOPTIC® (Timolol Maleate, MSD) after prolonged therapy has been reported in some patients. However, in one long-term study in which 96 patients have been followed for at least three years, no significant difference in mean intraocular pressure has been observed after initial stabilization.

Drug Interactions: Although TIMOPTIC used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with TIMOPTIC and epinephrine has been reported occasionally.

Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Caution should be used in the coadministration of beta-adrenergic blocking agents, such as TIMOPTIC, and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Animal Studies: No adverse ocular effects were observed in rabbits and dogs administered TIMOPTIC topically in studies lasting one and two years respectively.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year oral study of timolol maleate in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human oral dose* (1 mg/kg/day). Similar differences were not observed in rats administered oral doses equivalent to 25 or 100 times the maximum recommended human oral dose. In a lifetime oral study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages up to 60 mg timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/mL). In Ames tests, the highest concentrations of timolol employed, 5000 or 10,000 μg/plate, were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human oral dose.

Pregnancy: Pregnancy Category C: Teratogenicity studies with timolol in mice and rabbits at doses up to 50 mg/kg/day (50 times the maximum recommended human oral dose) showed no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (1,000 times the maximum recommended human oral dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 100 times the maximum recommended human oral dose, in this case without apparent maternotoxicity. There are no adequate and well-controlled studies in pregnant women. TIMOPTIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established by adequate and well-controlled studies.

ADVERSE REACTIONS: TIMOPTIC Ophthalmic Solution is usually well tolerated. The following adverse reactions have been reported either in clinical trials of up to three years' duration prior to release in 1978 or since the drug has been marketed.

BODY AS A WHOLE: Headache, asthenia, chest pain. CARDIOVASCULAR: Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, palpitation, cardiac arrest. DIGESTIVE: Nausea, diarrhea. NERVOUS SYSTEM/PSYCHIATRIC: Dizziness, depression, increase in signs and symptoms of myasthenia gravis, paresthesia. SKIN: Hypersensitivity, including localized and generalized rash, urticaria. RESPIRATORY: Bronchospasm (predominantly in patients with preexisting bronchospastic disease), respiratory failure, dyspnea, nasal congestion. ENDOCRINE: Masked symptoms of hypoglycemia in insulin-dependent diabetics (see WARNINGS). SPECIAL SENSES: Signs and symptoms of ocular irritation, including conjunctivitis, blepharitis, keratitis, blepharoptosis, decreased corneal sensitivity, visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis.

Causal Relationship Unknown: The following adverse effects have been reported, and a causal relationship to therapy with TIMOPTIC has not been established: *Body as a Whole:* Fatigue; *Cardiovascular:* Hypertension, pulmonary edema, worsening of angina pectoris; *Digestive:* Dyspepsia, anorexia, dry mouth; *Nervous System/Psychiatric:* Behavioral changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence, and other psychic disturbances; *Skin:* Alopecia; *Special Senses:* Aphakic cystoid macular edema; *Urogenital:* Retroperitoneal fibrosis, impotence.

The following additional adverse effects have been reported in clinical experience with oral timolol maleate and may be considered potential effects of ophthalmic timolol maleate: *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Edema, worsening of arterial insufficiency, Raynaud's phenomenon, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting; *Hematologic:* Nonthrombocytopenic purpura; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating, cold hands and feet; *Musculoskeletal:* Arthralgia, claudication; *Nervous System/Psychiatric:* Vertigo, local weakness, decreased libido, nightmares, insomnia, diminished concentration; *Respiratory:* Rales, cough, bronchial obstruction; *Special Senses:* Tinnitus, dry eyes; *Urogenital:* Urination difficulties.

Potential Adverse Effects: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents and may be considered potential effects of ophthalmic timolol maleate: *Digestive:* Mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Agranulocytosis, thrombocytopenic purpura; *Nervous System:* Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Urogenital:* Peyronie's disease.

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis sicca, otitis, and sclerosing serositis attributed to the beta-adrenergic receptor blocking agent practolol. This syndrome has not been reported with timolol maleate.

HOW SUPPLIED: TIMOPTIC Ophthalmic Solution, 0.25% and TIMOPTIC Ophthalmic Solution, 0.5%. Both are available in 2.5-mL, 5-mL, 10-mL, and 15-mL plastic OCUMETER® ophthalmic dispensers with a controlled drop tip. **Also Available:** Preservative-free TIMOPTIC in OCUDOSE® (Dispenser) Sterile Ophthalmic Unit-Dose Dispenser (see separate Prescribing Information).

Storage: Protect from light. Store at room temperature.

*The maximum recommended single oral dose is 30 mg of timolol. One drop of TIMOPTIC 0.5% contains about 1/150 of this dose, which is about 0.2 mg.

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For more detailed information, consult your MSD Representative and the Prescribing Information.
Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

J7TM26 (426/303)

INCOMPARABLE GLAUCOMA THERAPY TODAY

Monocular Diplopia Accompanying Ordinary Refractive Errors

Paul Coffeen, B.S.E.E., and David L. Guyton, M.D.

Monocular diplopia is commonly encountered in ophthalmic practice. We discovered that it could be induced in nine (82%) of 11 normal eyes with ordinary spherical or astigmatic defocus of the retinal image. Possible mechanisms responsible for this effect include retinal processing, diffraction effects, and spherical aberration. By employing geometric blur circle theory and using a simple optical model to photograph the effect, we concluded that monocular diplopia in the setting of ordinary refractive error is secondary to relatively minor optical irregularity such as spherical aberration. Contour enhancement properties of the retina probably accentuate this effect. Ordinary refractive error should therefore not be overlooked or discounted in patients with monocular diplopia.

© American Journal of Ophthalmology 105:451–459, May, 1988

A Clinical Index for Predicting Visual Acuity After Cataract Surgery

Marshall J. Graney, Ph.D., William B. Applegate, M.D., Stephen T. Miller, M.D., Janet T. Elam, B.S., Jerre M. Freeman, M.D., Thomas O. Wood, M.D., and Thomas C. Gettlefinger, M.D.

We developed a clinical index for predicting postoperative visual acuity of cataract patients and cross-validated it using data from 182 patients aged 70 years and older. The index consisted of four statistically combined indicators: age, preoperative visual acuity, frequency of reading, and comorbidity. Validation of the index included comparisons to two standard technical instruments for measurement of retinal visual acuity. For the clinical index, 72% of predictions were accurate within one Snellen line of postoperative visual acuity compared to 37% using a laser interferometer and 33% using a potential acuity meter. Testing of the clinical index's external validity using data from 111 patients in a different ophthalmology clinic disclosed 61% of predictions accurate within one Snellen line.

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Increased Intraocular Pressure in the Immediate Postoperative Period After Extracapsular Cataract Extraction

Jeffrey G. Gross, M.D., Dale R. Meyer, M.D., Alan L. Robin, M.D., Alfred A. Filar, M.D., and James S. Kelley, M.D.

We evaluated the immediate intraocular pressure increase after extracapsular cataract surgery in 58 eyes. Two to three hours postoperatively, 34 eyes (59%) developed an intraocular pressure greater than or equal to 25 mm Hg. We found an intraocular pressure of at least 40 mm Hg in seven eyes. Mean intraocular pressure two to three hours postoperatively was 8.9 ± 9.8 mm Hg greater than the preoperative intraocular pressure. The use of intraocular sodium hyaluronate had no apparent effect on intraocular pressure.

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Photocoagulation Treatment of Radiation Retinopathy

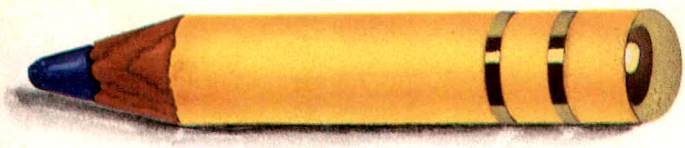
James L. Kinyoun, M.D., Mark E. Chittum, M.D., and Craig G. Wells, M.D.

We studied the visual and anatomic effects of focal photocoagulation for clinically significant radiation macular edema in five eyes of four patients and panretinal photocoagulation for proliferative radiation retinopathy in six eyes of three patients. Focal and limited scatter photocoagulation was successful in preventing further vision loss in all five eyes treated for macular edema. Three eyes treated with panretinal photocoagulation had regression of neovascularization. The other three eyes treated for proliferative retinopathy subsequently had dense vitreous hemorrhages that required vitrectomy for restoration of useful vision.

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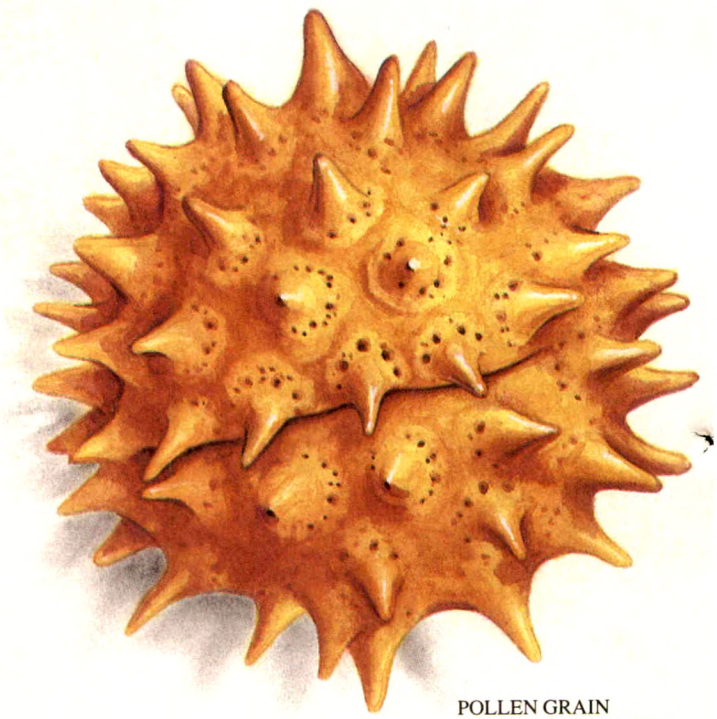
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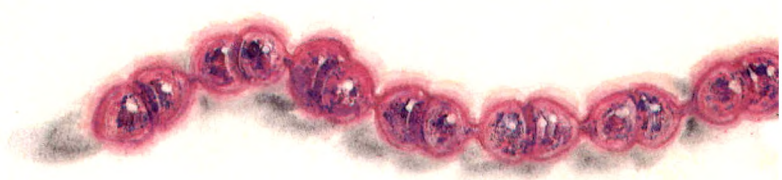
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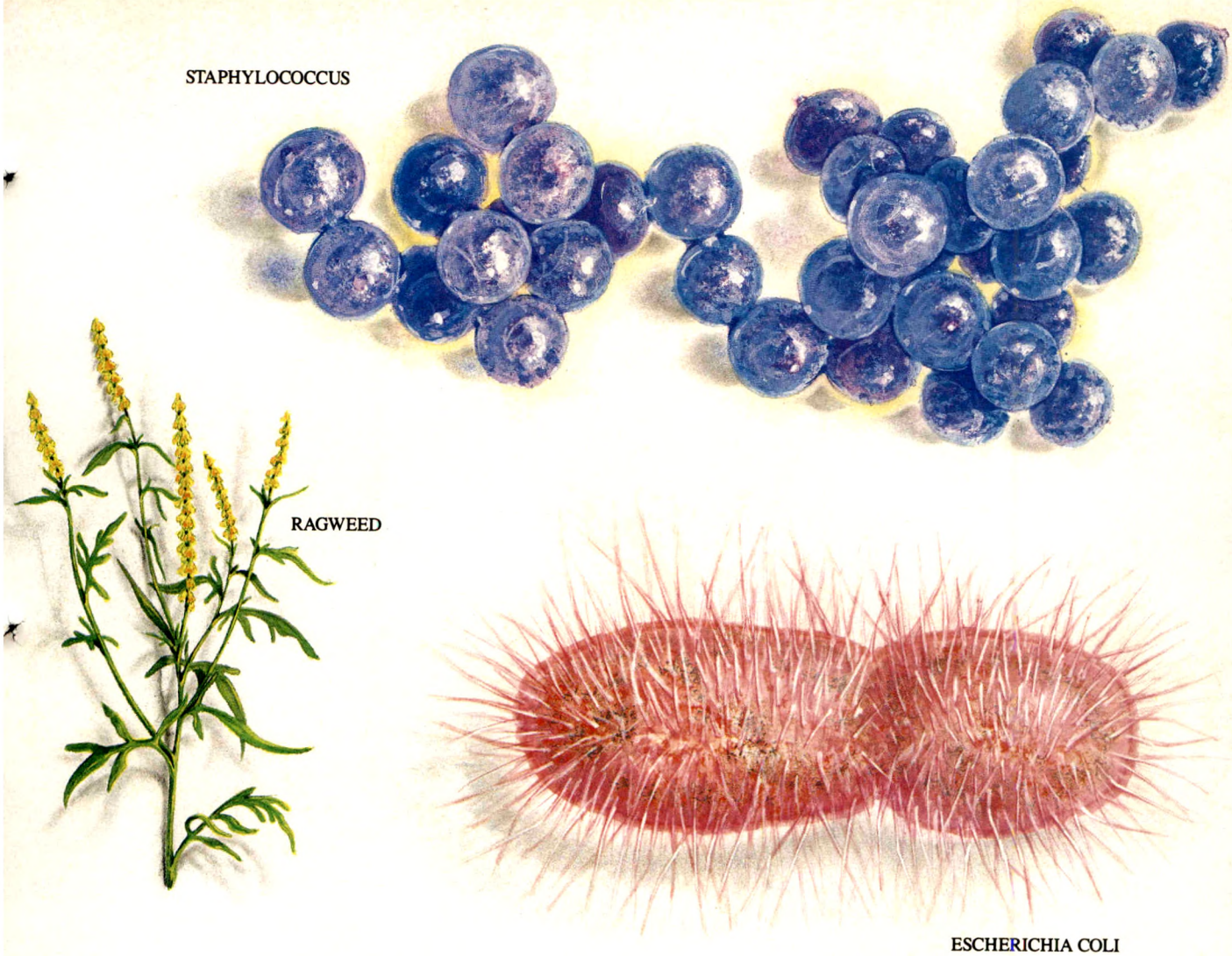
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[1]Reference: Allergan Pharmaceuticals Report Series, No. 188, 1982. The clinical significance of these animal data is unknown.

Please see adjacent page for brief summary of prescribing information.



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INDICATIONS AND USAGE: Bleph-10 is indicated for the treatment of conjunctivitis, corneal ulcer and other superficial ocular infections caused by susceptible microorganisms, and as adjunctive treatment in systemic sulfonamide therapy of trachoma.

CONTRAINDICATIONS: Bleph-10 is contraindicated in individuals who have a hypersensitivity to sulfonamide preparations or to any of the ingredients of the preparation.

PRECAUTIONS: Sulfacetamide preparations are incompatible with silver preparations.

Nonsusceptible organisms, including fungi, may proliferate with the use of this preparation. Sulfonamides are inactivated by the aminobenzoic acid present in purulent exudates. Sensitization may occur when a sulfonamide is re-administered irrespective of the route of administration, and cross-sensitivity between different sulfonamides may occur. If signs of sensitivity or other untoward reactions occur, discontinue use of the preparation.

ADVERSE REACTIONS: Sulfacetamide sodium may cause local irritation, stinging and burning. While the irritation may be transient, occasionally, use of the medication has to be discontinued.

Although sensitivity reactions to sulfacetamide sodium are rare, an isolated incident of Stevens-Johnson syndrome was reported in a patient who had experienced a previous bullous drug reaction to an orally administered sulfonamide, and a single instance of local hypersensitivity was reported which progressed to a fatal syndrome resembling systemic lupus erythematosus.

Blephamide

(sulfacetamide sodium - prednisolone acetate)
Liquifilm® sterile ophthalmic suspension

INDICATIONS AND USAGE: A steroid/anti-infective combination is indicated for steroid- responsive inflammatory ocular conditions for which a corticosteroid is indicated and where bacterial infection or a risk of bacterial ocular infection exists.

Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe where the inherent risk of steroid use in certain infective conjunctivitides is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

The particular anti-infective drug in this product is active against the following common bacterial eye pathogens: *Escherichia coli, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus (viridans group), Pseudomonas* species, *Haemophilus influenzae, Klebsiella* species, and *Enterobacter* species. This product does not provide adequate coverage against *Neisseria* species and *Serratia marcescens.*

CONTRAINDICATIONS: Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, and many other viral diseases of the cornea and conjunctiva. Mycobacterial infection of the eye. Fungal diseases of the ocular structures. Hypersensitivity to a component of the medication. (Hypersensitivity to the antimicrobial component occurs at a higher rate than for other components.)

The use of these combinations is always contraindicated after uncomplicated removal of a corneal foreign body.

WARNINGS: Prolonged use may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Prolonged use may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection. If these products are used for 10 days or longer, intraocular pressure should be routinely monitored even though it may be difficult in children and uncooperative patients.

Employment of a steroid medication in the treatment of herpes simplex requires great caution.

A significant percentage of staphylococcal isolates are completely resistant to sulfa drugs.

PRECAUTIONS: The initial prescription and renewal of the medication order beyond 20 milliliters should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

The possibility of fungal infections of the cornea should be considered after prolonged steroid dosing.

ADVERSE REACTIONS: Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component, or the combination. Exact incidence figures are not available since no denominator of treated patients is available.

Reactions occurring most often from the presence of the anti-infective ingredient are allergic sensitizations. The reactions due to the steroid component in decreasing order of frequency are: elevation of intraocular pressure (IOP) with possible development of glaucoma, and infrequent optic nerve damage; posterior subcapsular cataract formation; and delayed would healing.

Secondary infection: The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroid. The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used.

Secondary bacterial ocular infection following suppression of host responses also occurs.

FML

(fluorometholone) 0.1%
Liquifilm® sterile ophthalmic suspension

INDICATIONS AND USAGE: FML is indicated for the treatment of corticosteroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe.

CONTRAINDICATIONS: FML is contraindicated in the following conditions:

Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, and other viral diseases of the cornea and conjunctiva.

Tuberculosis of the eye.

Fungal diseases of the ocular structures.

Hypersensitivity to any component of the medication.

WARNINGS: Corticosteroid medication in the treatment of patients with a history of herpes simplex keratitis (involving the stroma) requires great caution; frequent slit lamp microscopy is mandatory.

Prolonged use may result in elevation of IOP, with damage to the optic nerve, defects in visual acuity and fields of vision, and/or in posterior subcapsular cataract formation. It may also aid in the establishment of secondary ocular infections from fungi or viruses liberated from ocular tissues.

Various ocular diseases and long-term use of topical corticosteroids have been known to cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation.

Acute purulent untreated infection of the eye may be masked or activity enhanced by the presence of corticosteroid medication.

PRECAUTIONS: General: As fungal infections of the cornea are particularly prone to develop coincidentally with long-term local corticosteroid applications, fungal invasion must be suspected in any persistent corneal ulceration where a corticosteroid has been used or is in use.

Intraocular pressure should be checked frequently.

Carcinogenesis, mutagenesis, impairment of fertility: No studies have been conducted in animals or in humans to evaluate the possibility of these effects with fluorometholone.

Pregnancy Category C: Fluorometholone has been shown to be teratogenic and embryocidal in rabbits when given in doses approximating the human dose and above. There are no adequate, well-controlled studies in pregnant women. Fluorometholone should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Fluorometholone was ocularly applied to both eyes of pregnant rabbits at various dosage levels on days 6 to 18 of gestation. A significant dose-related increase in fetal abnormalities and in fetal loss was observed.

Nursing Mothers: It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk, nevertheless, the physician should consider the patient discontinuing nursing while the drug is being administered.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Adverse reactions include, in decreasing order of frequency, elevation of intraocular pressure (IOP) with possible development of optic nerve damage; loss of visual acuity or defects in fields of vision; posterior subcapsular cataract formation; delayed wound healing.

The following have also been reported after the use of topical corticosteroids: Secondary ocular infection from pathogens liberated from ocular tissues and, rarely, perforation of the globe when used in conditions where there is thinning of the cornea or sclera.

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Comparison of Laser Beam Diameters
(focused at iris, beam diameters in mm)
50 micron setting

LENS	IRIS	CORNEA	RETINA
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Abraham lens	.032	.520	3.60
Wise lens	**.019**	**1.020**	**7.14**

Table: Laser beam convergence angle in air calculated at 8.5°.

Note: A laser with a 30 micron setting would produce an iris spot size of .011mm

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- anti-reflective coating maximizes light transmission.
- effective for Nd: YAG iridotomies and division of vitreous strands.

Ref. AJO, Vol. 101, No. 5, May 1986.

Designed by: James B. Wise, M.D.
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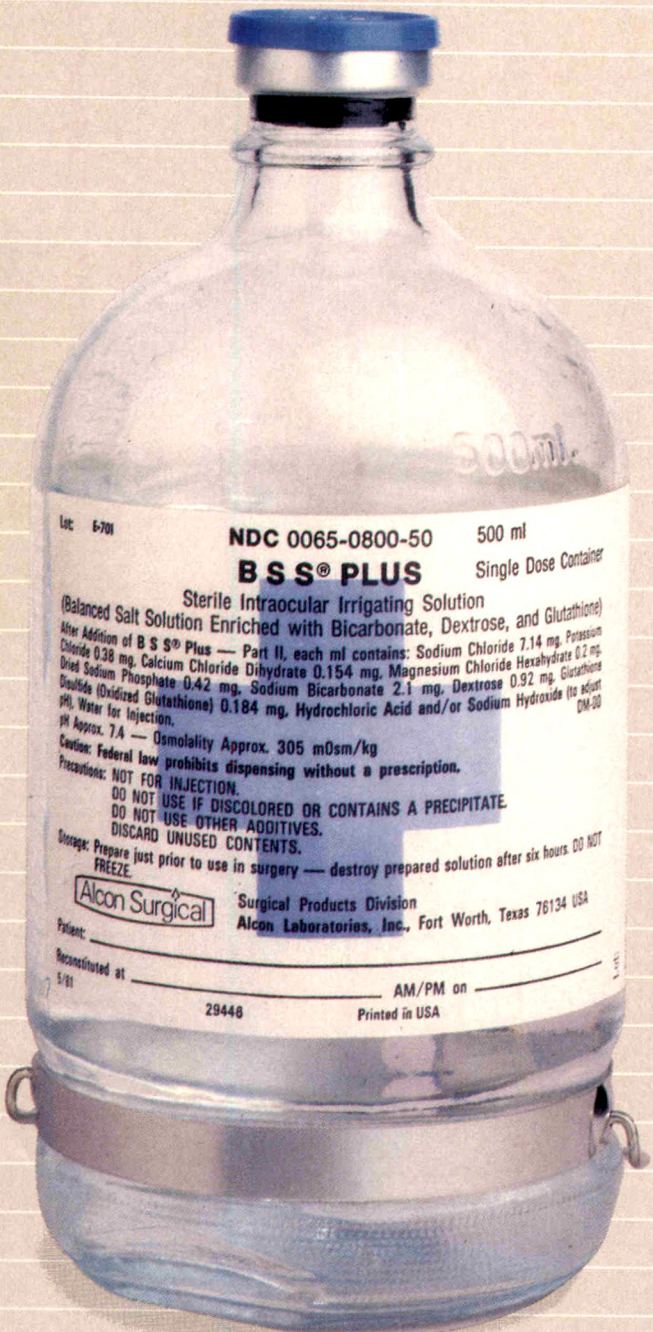
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The solution does not contain a preservative and should be prepared just prior to use in surgery.

Part I: A sterile 28.8 mL solution in a 30 mL single-dose plastic bottle or a sterile 480 mL solution in a 500 mL single-dose bottle to which the Part II concentrate is added. Each mL of Part I contains: Sodium Chloride 7.44 mg, Potassium Chloride 0.395 mg, Anhydrous Dibasic Sodium Phosphate 0.433 mg, Sodium Bicarbonate 2.19 mg, Hydrochloric Acid and/or Sodium Hydroxide (to adjust pH), in Water for Injection. DM-00

Part II: 30 mL size: A sterile concentrate in a 1.2 mL single-dose syringe for addition to Part I. 500 mL size: A sterile concentrate in a 20 mL single-dose vial for addition to Part I. Each mL of Part II contains: Calcium Chloride Dihydrate 3.85 mg, Magnesium Chloride Hexahydrate 5 mg, Dextrose 23 mg, Glutathione Disulfide (Oxidized Glutathione) 4.6 mg, in Water for Injection. DM-00

After addition of BSS PLUS® Part II to the Part I bottle, each mL of reconstituted product contains: Sodium Chloride 7.14 mg, Potassium Chloride 0.38 mg, Calcium Chloride Dihydrate 0.154 mg, Magnesium Chloride Hexahydrate 0.2 mg, Anhydrous Dibasic Sodium Phosphate 0.42 mg, Sodium Bicarbonate 2.1 mg, Dextrose 0.92 mg, Glutathione Disulfide (Oxidized Glutathione) 0.184 mg, Hydrochloric Acid and/or Sodium Hydroxide (to adjust pH), in Water for Injection.

The reconstituted product has a pH of approximately 7.4. Osmolality is approximately 305 mOsm/kg.

CONTRAINDICATIONS: There are no specific contraindications to the use of BSS PLUS,® however, contraindications for the surgical procedure during which BSS PLUS® is to be used should be strictly adhered to.

WARNINGS: For IRRIGATION during ophthalmic surgery only. BSS PLUS® is NOT for injection or intravenous infusion.

PRECAUTIONS: DO NOT USE BSS PLUS® UNTIL RECONSTITUTED. Do not use Part I if it does not contain a vacuum (500 mL size). Do not use additives other than Part II. Do not use if Part I, Part II or the reconstituted solution is discolored or contains a precipitate. SINCE BSS PLUS IS INTENDED FOR INTRAOCULAR IRRIGATION, IT DOES NOT CONTAIN A PRESERVATIVE AND, THEREFORE, SHOULD NOT BE USED ON MORE THAN ONE PATIENT. DISCARD ANY UNUSED SOLUTION SIX HOURS AFTER PREPARATION. Studies suggest that intraocular irrigating solutions which are iso-osmotic with normal aqueous fluids should be used with caution in diabetic patients undergoing vitrectomy since intraoperative lens changes have been observed.

There have been reports of corneal clouding or edema following ocular surgery in which BSS PLUS® was used as an irrigating solution. As in all surgical procedures, appropriate measures should be taken to minimize trauma to the cornea and other ocular tissues.

ADVERSE REACTIONS: Rarely, postoperative inflammatory reactions as well as incidents of corneal edema and corneal decompensation have been reported. Their relationship to the use of BSS PLUS has not been established.

OVERDOSAGE: The solution has no pharmacological action and thus has no potential for overdosage. However, as with any intraocular surgical procedure, the duration of intraocular manipulation should be kept to a minimum.

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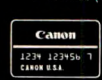
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Pascal Rol, Opt. Eng., Franz Fankhauser, M.D., and Sylwia Kwasniewska, M.D.

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Atypical Retinitis in Patients With the Acquired Immunodeficiency Syndrome

Mark T. Fay, M.D., William R. Freeman, M.D., Clayton A. Wiley, M.D., David Hardy, M.D., and Samuel Bozzette, M.D.

We examined three patients with AIDS who had large, sharply demarcated areas of thinned retina consistent with inactive cytomegalovirus retinitis and who were not treated with ganciclovir. These lesions appeared identical to clinically inactive areas of cytomegalovirus retinitis after effective antiviral treatment. All patients were receiving azidothymidine or ribavirin, or both, which have activity against the human immunodeficiency virus and which may improve immune function. All patients also received oral acyclovir at doses ineffective against cytomegalovirus retinitis.

© American Journal of Ophthalmology 105:483–490, May, 1988

Ultrastructural Characteristics of New Vessels in Proliferative Diabetic Retinopathy

John M. Williams, Sr., M.D., Eugene de Juan, Jr., M.D., and Robert Machemer, M.D.

We studied the ultrastructural characteristics of 23 vascularized preretinal membranes removed from 22 eyes during pars plana vitrectomy for proliferative diabetic retinopathy. Traction detachment of the macula was the most frequent reason for surgery (15 of 22 eyes), followed by nonclearing vitreous hemorrhage (seven of 22 eyes). Vessels found in the membranes were studied by serial sectioning and categorized as having either developing, mature, or regressing characteristics. Developing vessels were seen in ten of 23 membranes (43%), mature vessels in 19 of 23 membranes (83%), and regressing vessels in 13 of 23 membranes (57%). Endothelial fenestrations and cell separations were rare. With three-dimensional reconstruction, we found that new vessels often extended cytoplasmic processes into the extracellular matrix and that lumina were present even at the distalmost tips of the vessels. Solid cords of endothelial cells were not seen.

We concluded that in proliferative diabetic retinopathy, new vessels develop by a process of focal extracellar matrix degradation, generalized and exuberant extracellar matrix production, cytoplasmic microvillus extension into the extracellular matrix and active lumen formation.

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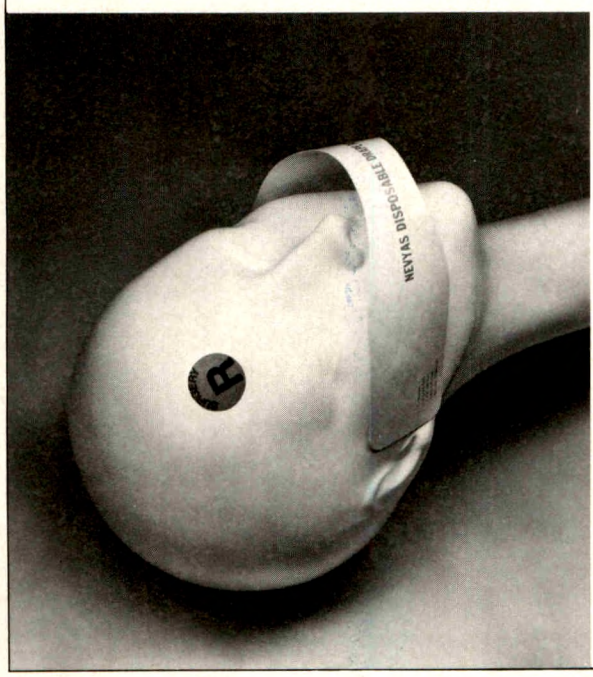
Narrow-Band Filtering for Monitoring Low-Amplitude Cone Electroretinograms in Retinitis Pigmentosa

Sten O. L. Andréasson, M.D., Michael A. Sandberg, Ph.D., and Eliot L. Berson, M.D.

Low amplitude (<10 μV) cone electroretinograms, elicited with 30-Hz white flicker from 59 patients with retinitis pigmentosa, were computer-averaged alone or in combination with a narrow-band electronic filter that increases the signal to noise ratio, thereby making it possible to evaluate the electroretinograms of most patients with retinitis pigmentosa. Narrow-band filtering reduced the amplitude of computer-averaged responses by an average of 7%, but the change in amplitude was independent of the size of the unbandpassed response. Narrow-band filtering also allowed measurement of 30-Hz cone responses in patients followed up over an 11- to 15-year period and quantitation of responses of less than 1 μV, which were not detectable with computer averaging alone.

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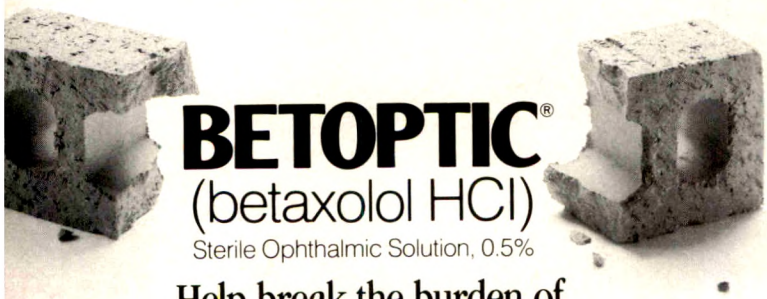
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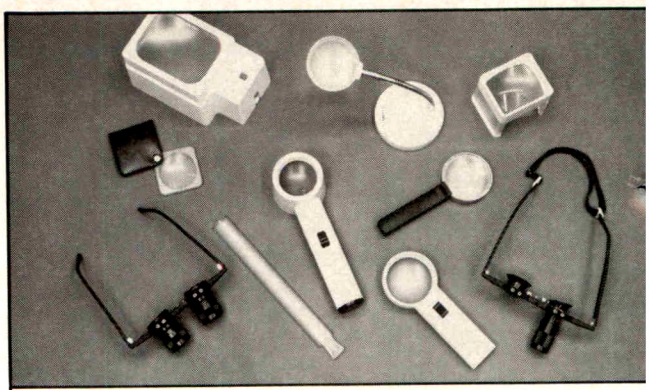
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Ocular: BETOPTIC Ophthalmic Solution has been well tolerated. Discomfort of short duration was experienced by one in four patients, but none discontinued therapy; occasional tearing has been reported. Rare instances of decreased corneal sensitivity, erythema, itching sensation, corneal punctate staining, keratitis, anisocoria and photophobia have been reported.

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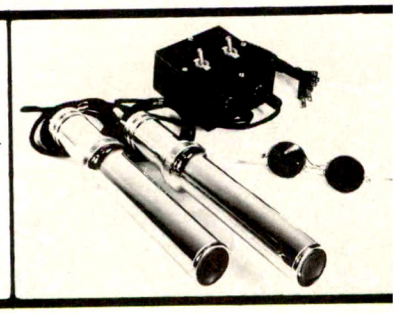
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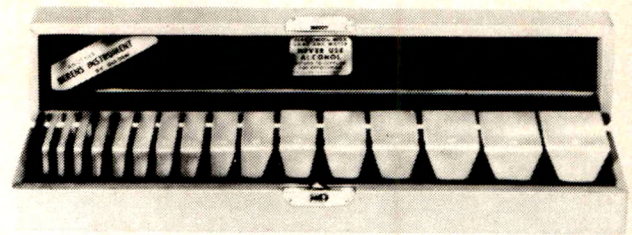
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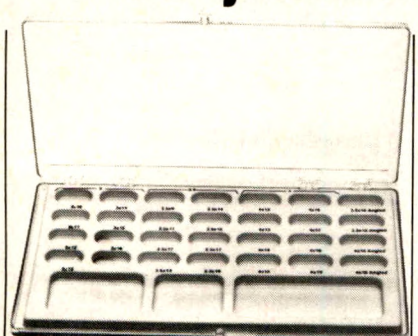
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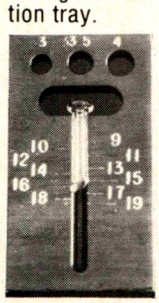
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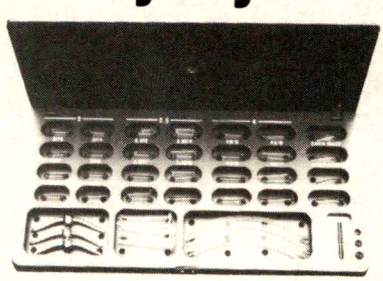
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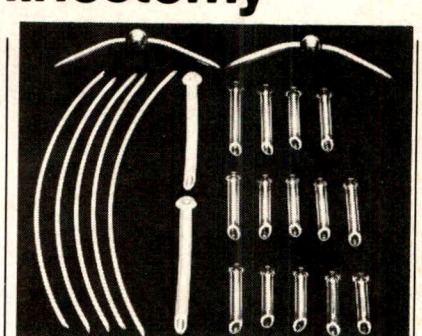
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Monocular Diplopia Accompanying Ordinary Refractive Errors

Paul Coffeen, B.S.E.E., and David L. Guyton, M.D.

Monocular diplopia is commonly encountered in ophthalmic practice. We discovered that it could be induced in nine (82%) of 11 normal eyes with ordinary spherical or astigmatic defocus of the retinal image. Possible mechanisms responsible for this effect include retinal processing, diffraction effects, and spherical aberration. By employing geometric blur circle theory and using a simple optical model to photograph the effect, we concluded that monocular diplopia in the setting of ordinary refractive error is secondary to relatively minor optical irregularity such as spherical aberration. Contour enhancement properties of the retina probably accentuate this effect. Ordinary refractive error should therefore not be overlooked or discounted in patients with monocular diplopia.

MONOCULAR DIPLOPIA has long been a perplexing problem in ophthalmic practice. Under certain conditions, up to 50% of normal individuals may experience monocular diplopia.[1] Most of the known mechanisms are optical ones such as irregular refraction, decentered contact lenses, double reflection from spectacle lenses, and the like. Neurologic causes are known but rare. Ordinary spherical or astigmatic refractive errors should not in theory cause monocular diplopia, but such errors, either uncorrected or incompletely corrected, have occasionally been reported as doing so.

By artificially inducing refractive errors in our eyes with trial lenses, we were surprised that monocular diplopia could be produced easily and repeatably. The question of how ordinary refractive error can generate monocular diplopia has not been completely investigated. Possible mechanisms include diffraction effects, retinal processing of blurred images, and optical irregularities that become manifest only in the presence of defocused images. Optical irregularities would include spherical aberration of the eye. Verhoeff,[2] writing in 1900 and furthering the work of Bull,[3] insightfully addressed the issue of spherical aberration as a cause of monocular diplopia. His theories have persisted since, last mentioned in a review by Amos.[4] Diffraction effects and retinal processing have not been previously implicated as causes of monocular diplopia. This study investigates the prevalence of monocular diplopia accompanying ordinary refractive error, and addresses the feasibility of various mechanisms.

Material and Methods

Prevalence study—To determine the prevalence of monocular diplopia accompanying refractive error, we used trial lenses to induce variable amounts of spherical refractive error in 11 eyes of nine subjects viewing radial patterns of black lines on white backgrounds. Two patterns of lines were used, the first being the stationary astigmatic dial target in the Reichert Ultramatic Project-o-Chart Projector, with each line width subtending approximately 1.5 minutes of arc at a viewing distance of 4 m. The second pattern was an astigmatic dial of inked lines on white posterboard with each line width subtending 2.8 minutes of arc at the 4-m dis-

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tance. An inked pattern was selected as well as a projected pattern to guard against possible aberrations generated by the projection process, which might yield spurious results. To test in both directions of defocus, both myopic and hyperopic refractive errors were induced using plus and minus spherical trial lenses, respectively. Dim room illumination was used with the projected pattern and normal bright room illumination with the inked pattern. Refractive correction was worn, so that each subject began at or near best corrected vision.

Subjects who had ostensibly normal eyes were selected, having presently corrected visual acuity better than or equal to 20/25. Ametropia was allowed, but subjects with any form of known ocular disease or symptoms of monocular diplopia were excluded. The subjects' ages ranged from 22 to 59 years. Three were nonpresbyopic, three were early presbyopic, and the remaining three were presbyopic.

For the subjects who were not presbyopic, either 0.5% or 1.0% tropicamide was instilled into one eye so that accommodation would not interfere with defocusing using minus spherical lenses. The early presbyopic subjects were first tested without cycloplegia, but tropicamide was added if significant accommodation occurred while defocusing with minus lenses. Cycloplegia was not used in the subjects who were presbyopic.

The subjects viewed the patterns monocularly. Best spherical correction was first determined by adding plus or minus spheres over the customary refractive correction. Defocusing was then begun from this null point. Slowly, in 0.25-diopter steps, first plus, then later minus, spherical lenses were introduced. The subject was asked to indicate if and when doubling or tripling of the lines, or simply blurring, occurred. If doubling occurred, the amount of defocus producing the most obvious doubling was determined. When the doubling was most distinct for only a few lines, that is, the doubling was not radially symmetric, the subject was asked to describe the remaining lines, whether clear, blurred, tripled, and the like. At each end point of testing, a pinhole aperture (1.0 mm in diameter) was introduced to verify the patient's responses, with the expectation that the doubling would disappear.

Testing for nonrefractive mechanisms—To determine whether the monocular diplopia we observed with induced refractive error might be caused by some type of retinal processing that enhanced or added edges to the blurred images, we produced blurred retinal images in optically corrected eyes. This was accomplished by purposefully blurring our projected astigmatic dial using spherical trial lenses placed before the projector lens. The pattern was observed as it was focused and defocused on the screen. We repeated this in the presence of induced refractive errors and while viewing through a pinhole aperture.

Photographic demonstration of the effects of spherical aberration—From the previous work of Verhoeff[2] and others,[5-8] it was evident that a likely cause for the type of monocular diplopia under study was spherical aberration of the eye's optics. We sought an objective demonstration of this phenomenon by photographing the effects of spherical aberration, replacing the camera lens with an ordinary positive spherical lens. Various drawings have been published by Tscherning[9] and others showing the effects of spherical aberration on blur circles and other defocused images. In 1900, Verhoeff[2] published a photograph of doubled letters that he had defocused with a positive spherical lens, but through a slit aperture. The slit aperture enhanced the effect of the doubling by limiting the doubling to only one direction.

For our photographs of blur circles, we used the full, circular aperture of an Asahi Pentax K-1000 single-lens reflex camera without an attached lens, using Kodak TRI-X Pan black and white film, ISO 125. The point source was approximated by a Sylvania 2-W tungsten arc lamp providing a source 0.178 mm in diameter. This was mounted against a black background, approximately 1 m from the camera. The luminance produced was controlled by neutral density filters when necessary. A +9-diopter (focal length, 111 mm) spherical plano-convex lens, 40 mm in diameter, was mounted in front of the lamp and was moved forward or backward along the optical axis to capture the image of the point source at various degrees of defocus. To allow for as much of the effect of the spherical aberration of the lens as possible, a wide aperture was maintained and exposure was controlled by varying shutter speed.

Attempts were made to photograph defocused images of inked black lines on white posterboard, but this object did not have enough contrast for the doubling effect to be suitably photographed. A higher-contrast object was produced by taping a black line on the surface of a rear-illuminated Plexiglas background. It was helpful to use a single blur circle to guide the amount of defocus produced, so

the tungsten arc lamp described above was centered behind a small hole drilled in the center of the black line target, surrounded by a black square to provide a suitable background for the single blur circle. The camera was used at a distance of approximately 1.2 m, using a +11.3-diopter (focal length, 88.5 mm) plano-convex lens, 51 mm in diameter, and Kodak Technical Pan film, ISO 100. An in-focus control photograph was taken using a 90-mm Vivitar Series I macro lens. Again, a wide aperture was maintained, and exposure was controlled by varying shutter speed and introducing neutral density filters in front of the lens when necessary.

Results

Prevalence study—Each of the nine subjects (11 eyes) reported doubling in at least one specific defocused condition. Also, in all subjects, the doubling disappeared when the pinhole aperture was introduced, with overall clearing of the image. The percentages of eyes experiencing doubling under different test conditions, and the average amounts of defocus required, are listed in the Table. The number of eyes experiencing radially symmetric doubling was one of 11 (9%) for induced myopia (plus lenses) and three of 11 (27%) for induced hyperopia (minus lenses).

Nonrefractive mechanisms—Defocusing the astigmatic dial pattern on the projector screen produced only blur, never doubling, as viewed by each of us. Induced refractive error, when the pattern was already defocused, only produced more blur. No doubling or edge enhancement was appreciated. Viewing through the pinhole aperture, whether the pattern was blurred on the screen or not, yielded no doubling.

Objective demonstration of the effect of spherical aberration—Figure 1 is a ray diagram showing the effects of positive (or undercorrected) spherical aberration on the image of a point source formed by a thin plus spherical lens with a circular aperture. Photographs taken with the apparatus described, at positions corresponding to a, b, and c in Figure 1, are shown from left to right in Figure 2. The pattern of light in Figure 2, left, with a dim center and bright surround, corresponding to position a in Figure 1, is the best candidate for creating apparent optical doubling in defocused images of extended objects. Note that perfect imaging of the point source is not possible because of the spherical aberration of the lens.

Figure 3 shows photographs of a black line and a central point source taken under three conditions: in focus without spherical aberration, in best focus with spherical aberration (position b of Fig. 1), and out of focus with spherical aberration (position a of Fig. 1). The diameter of the central blur circle in the out-of-focus photograph in Figure 3 is approximately 3.6 times the diameter of the in-focus black line. The defocused light from the background, overlapping in the center of the black line, creates an apparent doubling of the line.

Discussion

Monocular diplopia accompanying some type of refractive error has been described in recent years by Fincham (1963),[5] Scott (1974),[6] Stampfer and Tredici (1975),[7] Records (1980),[8] Guyton (1984),[1] and Amos (1986).[4] Our prevalence study demonstrates that ordinary refractive error yielding defocused retinal images is commonly and strongly associated with monocular diplopia of black lines on white backgrounds, occurring in greater than 60% of the

TABLE
PREVALENCE OF MONOCULAR DIPLOPIA ACCOMPANYING INDUCED REFRACTIVE ERRORS IN 11 EYES

	NO. OF EYES EXPERIENCING DOUBLING WITH INDUCED MYOPIA	NO. OF EYES EXPERIENCING DOUBLING WITH INDUCED HYPEROPIA	AVERAGE AMOUNT OF DEFOCUS (D)	STANDARD DEVIATION OF DEFOCUS (D)
Projected lines	9 (82%)	7 (63%)	+1.14/−1.57	0.47/0.43
Inked lines	9 (82%)	9 (82%)	+1.69/−2.19	0.89/0.83

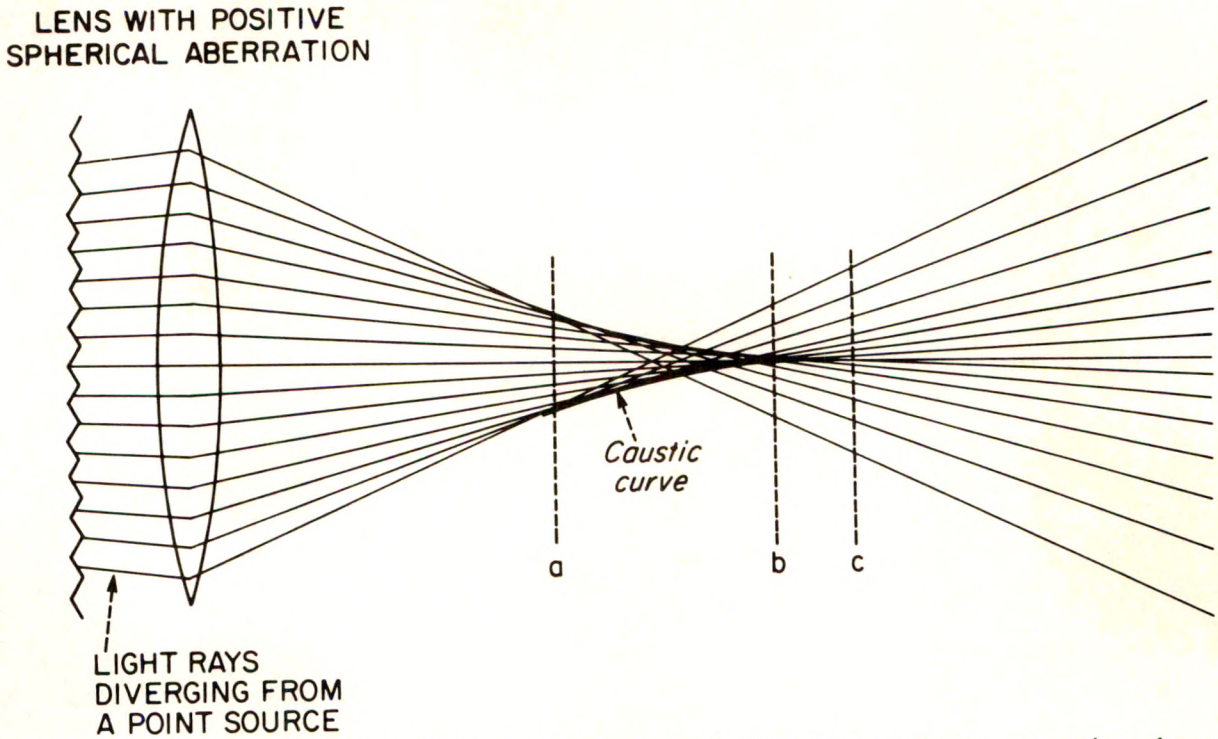


Fig. 1 (Coffeen and Guyton). Spherical aberration of a simple plus lens. The peripheral rays are refracted more strongly than the paraxial rays, creating different blur circles at positions a, b, and c. The caustic curve is the envelope that is tangent to each refracted light ray.

subjects tested with both induced myopia and induced hyperopia. When a pinhole was used to neutralize the effect of the defocusing lens, the diplopia disappeared with each subject. The clinical implications are clear. Ordinary refractive error should be a primary consideration in patients with monocular diplopia, especially because correction is easily accomplished. But what is the mechanism by which ordinary refractive error leads to monocular diplopia?

Diffraction effects as a cause of monocular diplopia can be ruled out because doubling was never seen through the pinhole aperture, whether or not in the presence of a refractive error or purposeful blurring of the test pattern.

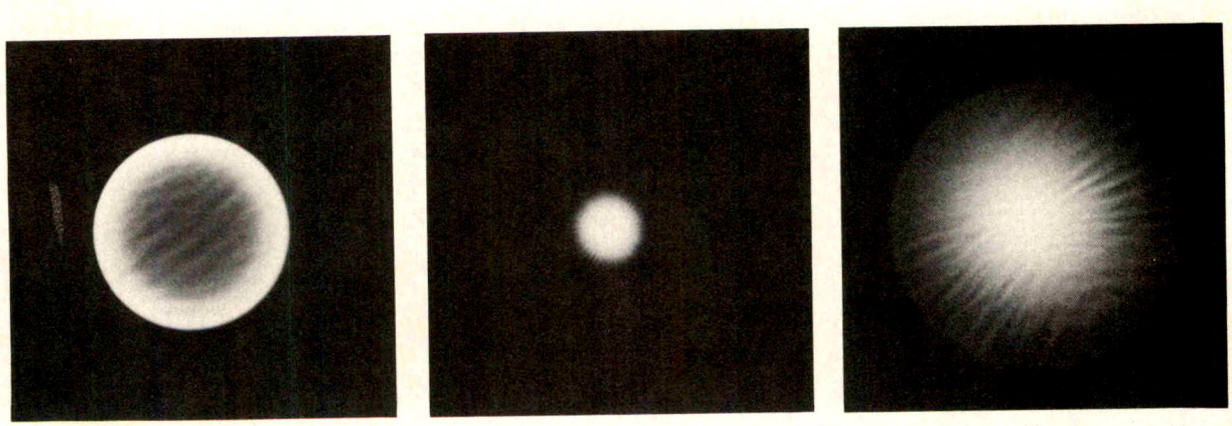


Fig. 2 (Coffeen and Guyton). Blur circle images of a point source of light photographed at positions corresponding to a, b, and c in Figure 1. The left image corresponds to position a, the middle image to position b, and the right image to position c.

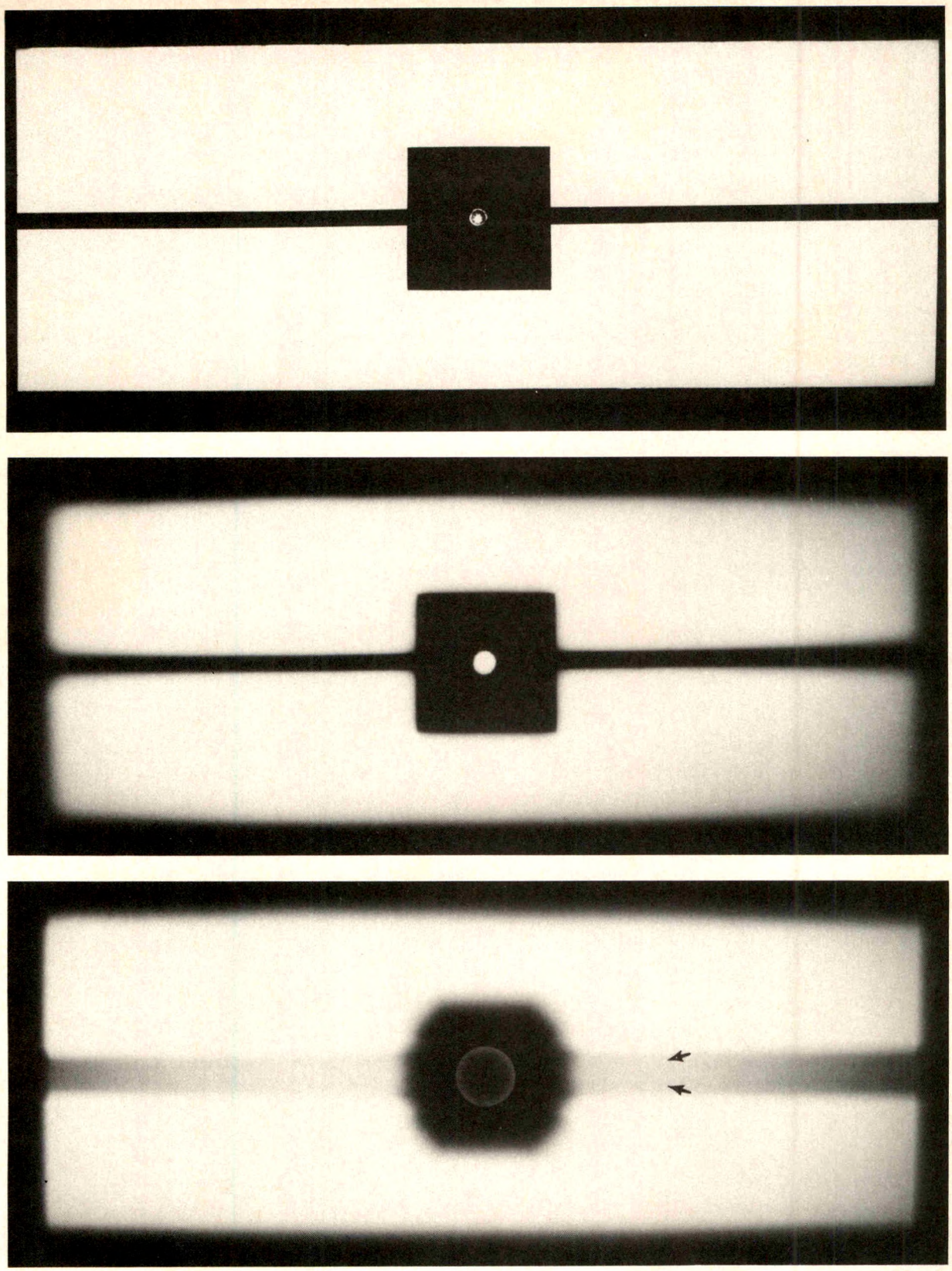


Fig. 3 (Coffeen and Guyton). Photographs of a rear-illuminated black line and a central point source, taken in best focus with a camera lens corrected for spherical aberration (top), in best focus with a simple plus lens having spherical aberration (middle), and out of focus with the simple plus lens (bottom). Note the apparent doubling of the black line in the bottom photograph (arrows).

Can retinal processing produce monocular diplopia? Part of the retina's function in visual processing is enhancement of contrast and the accentuation of contours.[10] An important example of this is the Mach band phenomenon. The idea of retinal processing as a principal mechanism creating monocular diplopia is appealing, but we believe this not to be the case. If retinal processing were the principal mechanism causing monocular diplopia of blurred retinal images accompanying refractive error, then one would expect to see some degree of doubling when viewing an already defocused object with an eye corrected for refractive error. This was not the case in our experiments; no doubling was observed under these conditions regardless of the amount of defocus of our projected test pattern on the projector screen. Therefore, how the defocusing occurs, that is, defocusing of the original object or defocusing via the eye, yields entirely different results. It is possible, however, that retinal mechanisms, specifically the Mach band phenomenon, may play some role in enhancing the monocular diplopia arising from refractive mechanisms.

Chromatic aberration of the trial lenses did not appear to play a role in the production of monocular diplopia. In our initial experimentation, we viewed the defocused lines through narrow band filters, and the doubling we observed persisted under these approximately monochromatic conditions.

Regular refractive errors can only produce uniform blur circles, not leading to monocular diplopia. Refractive aberration must be implicated, with spherical aberration being most consistent with the radial symmetry of several subjects' observations. Verhoeff[2] first proposed spherical aberration as the mechanism of doubling in defocused images. He used a ray diagram similar to that in Figure 1 to explain his theory. He also examined the cross sections of the image of a point source of light formed by a plus spherical lens having positive symmetric spherical aberration (as described by Tscherning[9] and as illustrated in Figures 1 and 2). Verhoeff theorized that if a point source is imaged as a ring of light, a line will be imaged as two lines. This would be true for a very narrow line consisting of a string of point sources. For short lines making up the strokes of letters, however, the situation is more complicated. Geometric blur circle theory can help explain the actual result.

A dark line on a light background can be thought of as the summation of two light/dark edges. Assume that the light part of the background is made up of a myriad of closely spaced point sources such that the space-averaged luminance of all the point sources is equal to the luminance of the background. Each point source, if imaged on a screen but defocused through a plus lens with positive spherical aberration, gives rise to a nonuniform blur circle (Fig. 4, a). The pattern of illumination in the blur circle, if the screen is placed

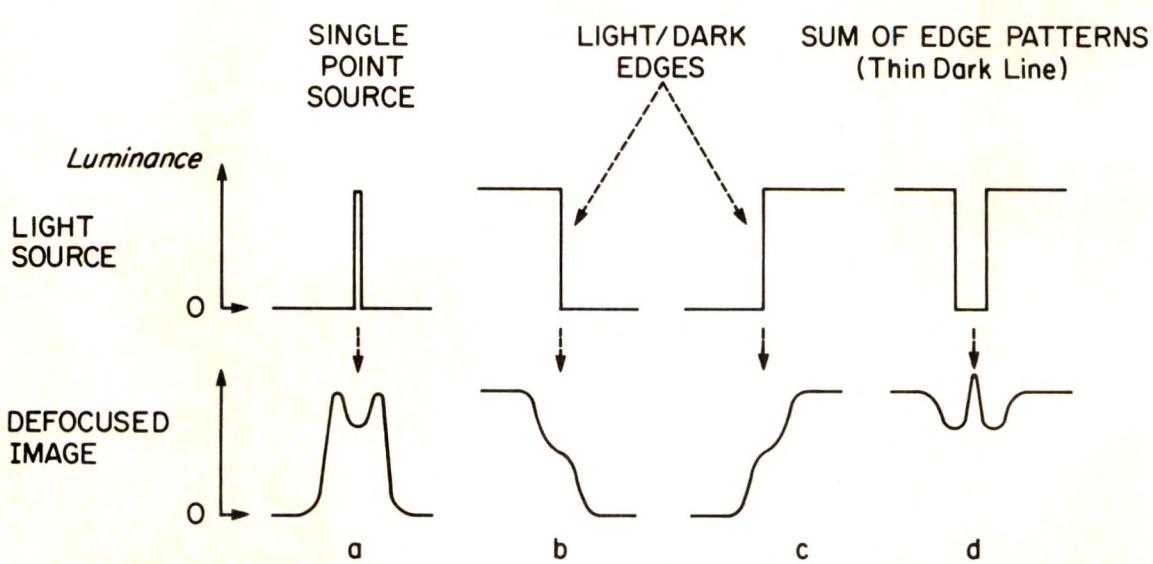


Fig. 4 (Coffeen and Guyton). Luminance distributions of light sources and defocused images of those sources, illustrating how the defocused images of two light/dark edges (b and c) can summate to produce a double, defocused line (d). This only occurs if the defocused image of the point source (a) is nonuniform, as produced, for example, by spherical aberration of the imaging system.

between the lens and the focal point of the marginal rays, will be similar to the pattern shown in Figure 2, left. Because the point sources making up the luminous background are noncoherent sources of light, the illumination patterns of the blur circles can be added linearly. Away from the edges of the line, the nonuniform blur circles add together to give uniform illumination. The edges of the dark line, however, are blurred (Fig. 4, b and c). The pattern of the nonuniform blur circle from each point of light determines the distribution of light in the blurred edges of the line, and the width of the blur circle determines the distance over which each edge is blurred. Given a certain amount of spherical aberration and defocus, the blurred edges add together to an illumination pattern as shown in Figure 4, d, having a peak of illumination in the center. If all the blur circles were uniform, there would be no doubling effect from overlap of the two blurred edges. It is the nonuniformity caused by aberration (spherical aberration in this case) and the amount of defocus that determine whether or not the doubling effect will be present. Although the aberrations of the human eye are much more complicated, this simple optical analysis seems to help explain what we observe in the human eye.

Photographic demonstration of the doubling phenomenon secondary to spherical aberration is shown in Figure 3, bottom. Because the size of the blur circle is approximately 3.6 times the width of the original dark line, significant overlap of the blurred edges of the defocused dark line occurred to produce the double image, more than required by the simple optical analysis presented above. Compared to what is seen by the human eye, the doubling as imaged on film is much less distinct. We theorize that the enhanced effect in the eye can be attributed to the contrast enhancement function of the retina.

Contrast enhancement of edges was first described by Ernst Mach over 100 years ago. Only in recent years, however, has the physiologic basis for the visual system's interpretation of edges been better understood. Much of the contrast enhancement effect involves the neural mechanism of lateral inhibition in the retina. The Mach band effect can be easily appreciated by viewing an in-focus border between light and dark. Along the dark side of the border a narrow, darker band appears, and along the light side of the border a lighter band appears, thereby enhancing the contrast of the border. The contours generated by the doubling phenomenon that we observe with spherical aberration are probably enhanced in the eye in the same way.

Remole[11] studied the relationship between the extent of edge enhancement and defocusing of the retinal image. He was able to demonstrate that the extent of edge enhancement (widening of the Mach band effect) does increase with defocus of the retinal image. Remole's subjects viewed a luminous bar variable in width. With the narrow bar defocused behind the retina such that the blur circles were comparable to the width of the bar, a doubling of the luminous bar was observed. This complication in Remole's experiment, that is, a drop in brightness in the center of the light band, was perceived by his subjects as "much greater than the undulations of light and dark typical of the border [Mach band] effects." Remole hypothesized that the effect observed could be explained by blur circles having cross sections with bimodal distributions, analogous to our explanation for the doubling observed of a black line on a white background.

An interesting finding from the prevalence study unexplainable on the basis of our photographic experiments is that monocular diplopia was experienced by observers under both myopic and hyperopic conditions. With our analysis of simple spherical optics, we have only demonstrated that monocular diplopia can occur with defocus that produces the blur circle pattern as seen in Figure 2, left. The luminance peaks in the periphery of this blur circle are formed by the intersection of marginal rays converging closer and closer to the lens along the optical axis. Note that this corresponds to the intersection of rays forming the caustic curve (Fig. 1). The optical model photographed in Figure 2 is consistent with this analysis.

We believe that the results of the prevalence study can be explained using geometric optics and ray diagrams, but only by taking into account more complex aberrations of the human eye. The spherical aberration of human eyes has been measured, but several different methods have yielded varying results.[12,13] Several generalizations can be made. Spherical aberration of the human eye varies from person to person, rarely shows axial symmetry, varies to a significant extent with accommodation, and deviates from that found in popular optical models of the eye.[14] Verhoeff[2] was most likely correct when he proposed that monocular diplopia found with defocus in both directions is caused by areas of both undercorrected and

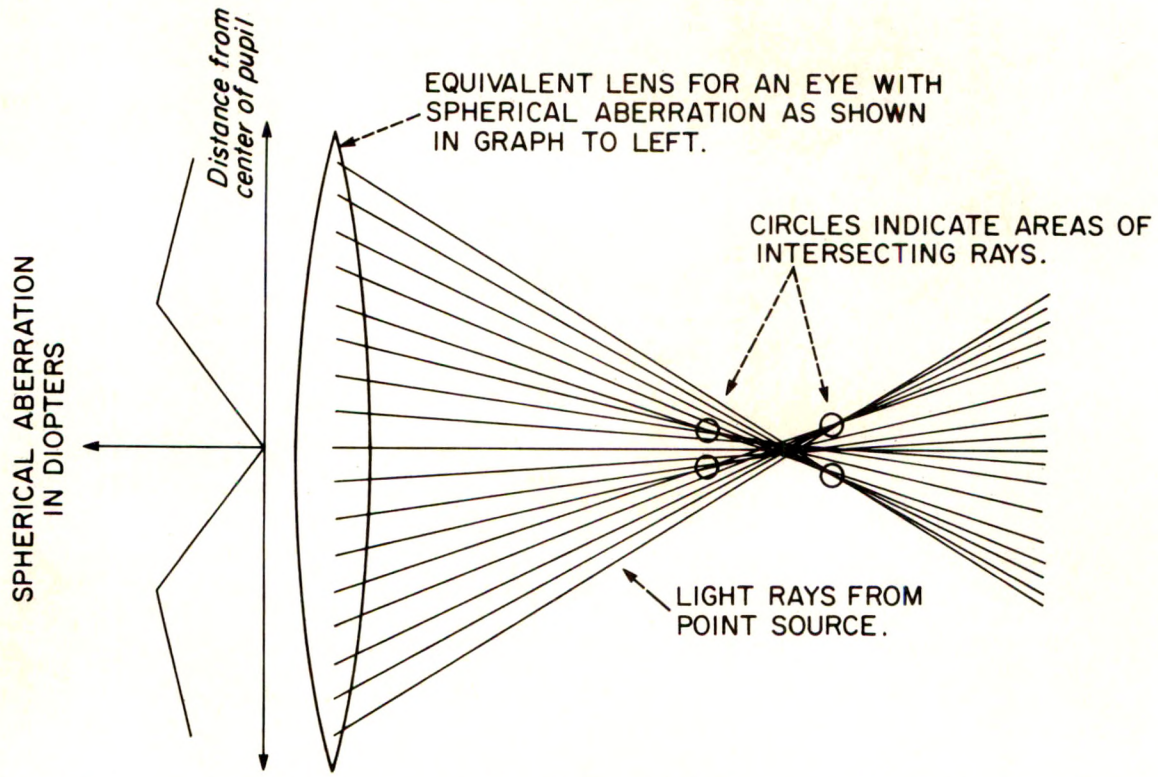


Fig. 5 (Coffeen and Guyton). Ray diagram illustrating how double imagery can be produced on each side of best focus, given the appropriate amount and form of spherical aberration.

overcorrected spherical aberration across the entrance pupil of the eye. A ray diagram in his paper illustrates how this could occur if one annular area of the entrance pupil had positive spherical aberration and another had negative spherical aberration. However, the data from experiments measuring the spherical aberration of the eye are not consistent with this, for the spherical aberration of the eye remains positive across the entrance pupil in most adult eyes. Suppose, however, that the spherical aberration at the edges of the entrance pupil became less positive than the peak value. Figure 5 shows a ray diagram using a hypothetical eye having such a distribution of spherical aberration (dimensions are exaggerated for illustration). It is evident that there are areas of intersecting rays on both sides of best focus (hyperopic and myopic conditions), which, by the geometric arguments presented above, would explain the results of the prevalence study.

We have shown how ordinary refractive error, in the presence of the relatively minor spherical aberration present in most eyes, can cause monocular diplopia. The phenomenon was readily induced in nine of 11 (82%) of the eyes of our normal subjects. The photographic simulation of monocular diplopia in the presence of spherical aberration can be explained by blur circle analysis. The contrast enhancement property of the eye (Mach band effect) does not appear sufficient to cause monocular diplopia by itself, but Mach bands may possibly enhance the appreciation of monocular diplopia from optical causes. More complicated spherical or other optical aberrations of the eye are necessary to explain the monocular diplopia experienced with defocused images on both sides of best focus as reported by most of our subjects. One possible pattern of aberration for doing this is illustrated in Figure 5.

Because of its high prevalence and ease of correction, refractive error should not be overlooked as a contributing cause of monocular diplopia. Early correction of refractive error in the evaluation of a patient complaining of monocular diplopia may provide a quick solution, obviating the need for more extensive investigation.

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OPHTHALMIC MINIATURE

Excision of the upper fourth of the iris, for glaucoma, was performed in three cases. In two of them, both eyes were operated upon simultaneously. Hardly an inflammatory symptom followed the operations, but vision was not improved. The ophthalmoscopic appearances in all were cupping of the entrance of the optic nerve, partial loss of transparency of the retina, etc. The patients were of the ages of 70, 64, and 60; vision had been lost gradually and without pain. The consistence of three of the globes was normal; three were harder. The pupils were inactive; their areae were greenish; there were no enlarged ciliary veins.

C. Baden, "Royal London Ophthalmic Hospital, Moorfields. Report of operations performed from February 1st to March 1st, 1858." *British Medical Journal*, March 27, 1858, p. 240.

A Clinical Index for Predicting Visual Acuity After Cataract Surgery

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We developed a clinical index for predicting postoperative visual acuity of cataract patients and cross-validated it using data from 182 patients aged 70 years and older. The index consisted of four statistically combined indicators: age, preoperative visual acuity, frequency of reading, and comorbidity. Validation of the index included comparisons to two standard technical instruments for measurement of retinal visual acuity. For the clinical index, 72% of predictions were accurate within one Snellen line of postoperative visual acuity compared to 37% using a laser interferometer and 33% using a potential acuity meter. Testing of the clinical index's external validity using data from 111 patients in a different ophthalmology clinic disclosed 61% of predictions accurate within one Snellen line.

PATIENTS UNDERGOING cataract surgery who have coincident retinal disease are at increased risk of unsuccessful outcomes. It is therefore important that the ophthalmologist be able to identify those who have retinal disease that might limit postoperative visual acuity.[1,2] Ophthalmoscopic examination for the diagnosis of retinal disease may, however, be limited in patients with advanced opacification of ocular media. To address this limitation technical instruments to estimate retinal visual acuity have been developed, including the laser interferometer and the potential acuity meter. However, this technology is not available to all clinicians, and the accuracy of technical instruments for predicting surgical outcomes has been questioned.[3,4] When technical instruments are developed for predicting clinical outcomes, an important part of technologic assessment is to compare accuracy of technical instrument prediction with either a clinical predictive index or with clinician judgment. The value of a nontechnical index for predicting the outcome of cataract surgery is unknown. The purpose of this study was to construct and test an index of a battery of standard clinical variables, and to compare its accuracy with that of standard technical instruments currently being used.

Subjects and Methods

Patients aged 70 years and older from two ophthalmology practices who were scheduled for cataract surgery between April 1983 and June 1984 were eligible for the study. Informed consent was obtained from all patients enrolled in the study. Patients who elected not to have surgery, those whose postoperative care was to be provided by another ophthalmologist, or those whose mental status did not allow them to cooperate with an interview were not eligible. Of 419 potential candidates for the study, 293 (70%) were enrolled, 42 (10%) refused to participate, and 84 (20%) were not enrolled because an interviewer was not available at the time of their surgery. A random sample of 100 charts of the 126 eligible patients who were not enrolled showed no significant differences between study participants and nonparticipants with regard to age, race, sex, or preoperative or postoperative visual acuity.

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Of 293 patients enrolled, 182 were from clinic A, a large private practice; and 111 were from clinic B, a university-affiliated practice. A clinical prediction index was developed using data from one clinic (training data), cross-validated, and evaluated for external validity using data from the second ophthalmology clinic (test data). Clinic A data were used as training data; 25 of these patients were excluded from data analysis because of the following: death (one patient), lost to follow-up (two patients), or retinal disease diagnosed preoperatively by ophthalmoscopy (22 patients). Clinic B data were used as the test data set; 15 of these patients were excluded from analysis because of retinal disease diagnosed preoperatively by ophthalmoscopy. Retinal disease has been established as a major predictor of unsuccessful cataract surgery.[3] These patients were, therefore, excluded from data analysis because they were at known increased risk of surgical failure and lower levels of postoperative visual acuity.

Interviews were conducted before surgery in the ophthalmologists' office or in the hospital by one of three trained interviewers. Follow-up interviews were conducted when vision had stabilized, approximately four months after surgery. A more detailed explanation of the methods has been published previously.[5]

Presurgical data included Snellen visual acuity, estimated retinal visual acuity using technical instruments, demographic data, and information about physical and mental function. Technical and clinical data about visual acuity were obtained from patients' ophthalmologic records. Best corrected monocular preoperative and postoperative visual acuity at four months were measured using an illuminated Snellen chart. Prognostic estimates of postoperative visual acuity were obtained by using both laser interferometer and potential acuity meter. A laser interferometer was used to estimate retinal interferometric visual acuity. A potential acuity meter was used to estimate retinal Snellen visual acuity. The operating principles and specifications of these instruments are described elsewhere.[6] Experienced ophthalmic technicians who were trained in the use of both the laser interferometer and potential acuity meter made and recorded the technical instrument measurements.

Except as otherwise noted, visual acuity was expressed as a decimal equivalent for data analysis (for example, 20/40 = 0.50).

Review of preoperative data identified 16 potential variables for inclusion in a clinical prediction index. These variables were considered representative of seven categories of potential indicators of postoperative visual acuity: (1) demographic (age), (2) social resources (economic status, availability of help in the home, availability of transportation), (3) subjective well-being (exercise, emotional status[7]), (4) morbidity (recent hospitalization, recent reported illnesses, number of current prescription medications), (5) general functional health (continence, total functional assessment inventory score,[7] instrumental activities of daily living[7]), (6) vision-related functions (driving, newspaper reading, watching television), and (7) preoperative vision (Snellen visual acuity).

A predictive index was developed using multivariate linear regression analysis[8] of postoperative visual acuity on candidate predictor variables. This analysis identified seven predictor variables whose regression coefficients explained 37% variance in postoperative visual acuity. These seven variables were (1) age, (2) preoperative Snellen visual acuity, (3) number of current prescription medications, (4) newspaper reading, (5) instrumental activities of daily living, (6) ability to drive an automobile, and (7) total functional assessment inventory score.

As the final step in index development, four predictor variables were selected that were considered both practical for widespread clinical use and statistically correlated ($P \leq .05$) to postoperative visual acuity: age, preoperative Snellen visual acuity, number of current prescription medications, and newspaper reading. Instrumental activities of daily living and total functional assessment inventory scores were not included because these multi-item scales were judged too cumbersome for inclusion in a simple clinical index. Ability to drive an automobile was deleted because it was relatively collinear with other predictor variables and added only slightly to variance explained in postoperative visual acuity. The four variables included in the clinical index explained 16% of variance in postoperative visual acuity measurements. The clinical index formula was as follows: predicted postoperative visual acuity = 1.60 − 0.0125(age) + 0.260(preoperative Snellen visual acuity) − 0.0317(number of current prescription medications) − 0.0214 (newspaper). Newspaper reading data were coded as follows: daily = 1.0, several times each week = 2.0, once a week = 3.0, occasionally = 4.0, never = 5.0.

Results

Of the 293 patients who underwent cataract surgery, follow-up visual acuity measurements at four months were available for 290 (99%). Statistical tests for differences in sample means comparing clinic A and clinic B found no contrasts that were either significant or that approached statistical significance (Table 1).

The clinical index, laser interferometer, and potential acuity meter were first assessed in terms of precision (the ability to predict postoperative visual acuity exactly). The results of this analysis indicated that the clinical index was precisely correct in predicting 32% of postoperative visual acuities in clinic A, a significant increase in precision compared to 14% for the laser interferometer and 15% for the potential acuity meter (both contrasts, $P \leq .001$) (Table 2).

The clinical index was significantly correlated with postoperative visual acuity ($r = .403$ $P \leq .001$), explaining 16% of variance (Table 2). The correlations of laser interferometer and potential acuity meter measurements to postoperative visual acuity were also statistically significant, but explained only 4% and 3% of variance, respectively.

When the error rate of the clinical index was compared to that of the laser interferometer and the potential acuity meter in clinic A data, the clinical index demonstrated a higher percent accuracy in predicting postoperative visual acuity both within one line (both contrasts, $P \leq .001$) and within two lines (both contrasts, $P \leq .001$). Furthermore, both the laser interferometer and the potential acuity meter significantly underestimated postoperative visual acuity in comparison to the clinical index (assessed at plus or minus one Snellen line of postoperative visual acuity; both contrasts, $P \leq .001$).

Postoperative visual acuity of 0.50 (20/40) or better has been recognized as a criterion of successful cataract surgery.[9] Thus, we used a postoperative Snellen visual acuity of 0.50 or greater as a criterion of surgical success to assess predictive accuracy, sensitivity, specificity, predictive value positive, and predictive value negative for both technical and clinical predictions using training data and test data (Table 2). The data of only those patients for whom the technical instruments produced Snellen-equivalent decimal visual acuities were used for assessing predictive validity in terms of these statistical measures; patients with instrument data such as pattern perception or light perception were excluded from this part of the analysis.

According to this criterion of success, 28% of patients were predicted to have successful surgery by the laser interferometer and 37% by the potential acuity meter, in contrast to 95% by the clinical index (the clinical index did not predict anyone to have a visual acuity below 0.125). Potential acuity meter predictions of good postoperative visual acuity have been found to be reliable, but predictions of poor

TABLE 1
PATIENT CHARACTERISTICS

VARIABLES	CLINIC A (N = 157)*	CLINIC B (N = 96)†	TOTAL (N = 253)
Age (mean ± S.D.)	77.2 ± 4.90	76.6 ± 4.92	77.0 ± 4.91
Sex ratio (M/100F)	30.8	31.5	31.1
Race (% white)	97.5	94.8	96.4
Preoperative visual acuity‡ (mean ± S.D.)	0.206 ± 0.161	0.164 ± 0.143	0.190 ± 0.154
Postoperative visual acuity‡ (mean ± S.D.)	0.616 ± 0.210	0.493 ± 0.179	0.569 ± 0.202
Comorbidity§ (mean ± S.D.)	1.13 ± 1.04	1.87 ± 1.51	1.41 ± 1.22
Newspaper reading¶ (mean ± S.D.)	1.76 ± 1.33	2.58 ± 1.89	2.07 ± 1.54

*Of 182 patients, one died, two were lost to follow-up, and 22 were excluded because of preoperatively diagnosed retinal disease.

†Of 111 patients, 15 were excluded because of preoperatively diagnosed retinal disease.

‡Eyes with nondecimal visual acuity measurements were excluded from arithmetic computations.

§Number of current prescription medications.

¶Daily = 1.0, several times each week = 2.0, once a week = 3.0, occasionally = 4.0, never = 5.0.

TABLE 2
ASSESSMENTS OF PREDICTIVE VALIDITY

STATISTICAL METHOD	CLINIC A			CLINIC B
	POTENTIAL ACUITY METER	LASER INTERFEROMETER	CLINICAL INDEX	CLINICAL INDEX
Pearson r*†	.210§	.185¶	.403‖	.286§
Precision*	15.3	13.7	31.5	25.3
Sensitivity‡	49.5	42.9	96.2	90.9
Specificity‡	80.9	90.0	22.7	26.0
Accuracy‡	54.8	50.8	85.6	70.1
Predictive value positive‡	92.7	95.4	55.6	60.0
Predictive value negative‡	24.6	24.3	88.4	68.7
Error rate*				
± 1 Snellen line	66.7	63.2	28.2	39.1
+1 Snellen line	5.8	7.2	15.5	32.2
−1 Snellen line	60.9	55.9	12.7	6.9
± 2 Snellen lines	41.3	44.1	9.9	24.1

*Criterion was four-month postoperative Snellen visual acuity expressed as a decimal fraction.
†Nondecimal visual acuity data were excluded from computations.
‡Criterion was surgical success: four-month postoperative Snellen visual acuity ≥ 0.5 vs failure (< 0.50).
§$P \leq .01$.
¶$P \leq .05$.
‖$P \leq .001$.

visual acuity were not accurate.[9] According to Minkowski, Palese, and Guyton,[9] technical instrument error rates increase with decreased levels of visual acuity. Thus, analysis of prediction errors in different ranges of predicted visual acuity was used to further assess operating characteristics of the clinical index, laser interferometer, and potential acuity meter. This analysis compared the arithmetic means of absolute values of errors of prediction across five visual acuity ranges for each predictive instrument, using categories similar to those used in previous reports.[4,9,10] Category cutoff points corresponding to visual acuity octaves were used to establish an objective criterion for categorization: I = 0.50 or better, II = 0.25 to below 0.50, III = 0.125 to below 0.25, IV = all fractional visual acuities below 0.125, and V = four levels of nonfractional visual acuity (counting fingers or pattern perception, hand motions, light perception, and no light perception). The results demonstrated substantially lower average clinical index prediction error in visual acuity ranges III through V, and no significant differences between methods of prediction for predictions of visual acuities of 0.25 or better (Figure).

To further evaluate precision, accuracy, and error rates, the clinical index was assessed using clinic B data. Neither the laser interferometer nor the potential acuity meter were used in clinic B, so direct comparisons between clinical index, laser interferometer, and potential acuity meter were not possible. Precision of clinical index predictions for clinic B patients was found to be 25% exact prediction, with 61% of predictions correct within one line and 76% within two lines of postoperative visual acuity. There was a 7% false-negative error rate and a 32% false-positive error rate, both assessed at plus or minus one Snellen line.

Instruments generally perform better with training data from which they were developed than with test data. Thus, when cross-validation using training data and external validation using test data were compared, the performance of the clinical index decreased in the second clinic, explaining 16% of clinic A postoperative visual acuity variance, and 8% of variance in clinic B. Nonetheless, the clinical index performed better in terms of precision, sensitivity, magnitude of correlation, accuracy, and predictive value negative in clinic B than did either the laser interferometer or potential acuity meter in clinic A.

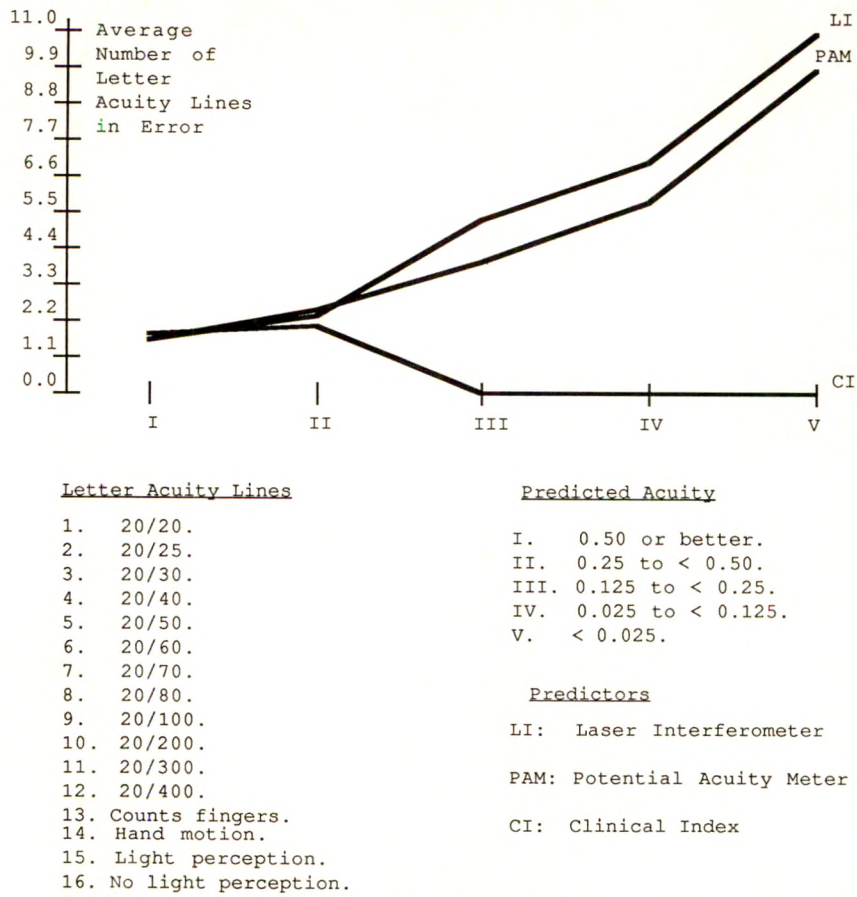


Figure (Graney and associates). Average prediction error by level of predicted visual acuity.

Discussion

This clinical index was 72% accurate in predicting postoperative visual acuity within one Snellen line for patients undergoing cataract surgery. Analysis of these data found the clinical index to be more accurate than two sophisticated instruments used to predict postoperative visual acuity, a laser interferometer and a potential acuity meter. When the clinical index was applied to test data from a second sample it was 61% accurate in predicting postoperative visual acuity within one Snellen line.

Media opacity that militates against ophthalmoscopic assessment of the fundus appears also to impair technical instrument assessments.[10,11] Thus, the most valuable contribution that the clinical index may make is with regard to estimating postoperative visual acuity for eyes predicted by technical instruments to have a postoperative visual acuity below 0.50. At levels of predicted visual acuity below 0.50 it is known that technical instruments are inaccurate and unreliable,[3,4,9] although a precise cutoff point for acceptable reliability has not been established.

With regard to predicting accurately both cataract surgery success and failure, an optimum protocol could require technical instrument assessment with selective follow-up using the clinical index for those patients predicted to be at increased risk of surgical failure. Technical instrument retinal visual acuity measurements of 0.50 or better predicted surgical success correctly 90% of the time (Table 2). However, the instruments' retinal visual acuity measurements below 0.50 were not predictive of surgical outcome for three of every four patients predicted to be at increased risk for surgical failure. Negative predictions were more reliably obtained using the clinical index;

two of every three predictions below 0.50 obtained using the clinical index were correct predictions of surgical failure.

We conclude from these findings that a clinician can obtain valuable information from a structured clinical index for predicting postoperative visual acuity for older cataract patients. The simple clinical index derived from prospective data in this study may be easily used by a clinician and may have greater accuracy than certain technical instruments.

There are several limitations to this study. First, the clinical index was originally developed in one ophthalmology practice where two ophthalmologists saw most patients. All patients were elderly, and almost all were white and from middle- or upper-class families. Therefore, the ability to generalize to other populations may be limited. The index was validated using a second clinical sample, but this second sample had similar demographic characteristics. Therefore, this or another clinical index needs to be further tested on other sample populations to establish broad generalizability. Nevertheless, the clinical index described herein was developed using a larger sample than that used earlier in similar studies of predictive accuracy, and the index can be expected to show operating characteristics in new settings similar to those reported here.

The index provides a formalization to the intuitiveness of a clinician's judgment. All clinicians recognize that technical instruments may provide misleading information, and that a clinical estimate may be more accurate in some patients. We identified which data a clinician may wish to use in making predictions of postoperative visual acuity for cataract patients, particularly for those at high risk of surgical failure.

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OPHTHALMIC MINIATURE

It made him hot to think what the Chief Butler's opinion of him would have been, if that illustrious personage could have plumbed with that heavy eye of his the stream of his meditations.

F. G. de Fontaine, *The Fireside Dickens*
New York, Dillingham, 1888

Increased Intraocular Pressure in the Immediate Postoperative Period After Extracapsular Cataract Extraction

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We evaluated the immediate intraocular pressure increase after extracapsular cataract surgery in 58 eyes. Two to three hours postoperatively, 34 eyes (59%) developed an intraocular pressure greater than or equal to 25 mm Hg. We found an intraocular pressure of at least 40 mm Hg in seven eyes. Mean intraocular pressure two to three hours postoperatively was 8.9 ± 9.8 mm Hg greater than the preoperative intraocular pressure. The use of intraocular sodium hyaluronate had no apparent effect on intraocular pressure.

ACUTE INCREASES in intraocular pressure after cataract extraction have been documented for over 20 years. The use of alpha-chymotrypsin during intracapsular cataract extraction was first associated with this complication.[1] Rich, Radtke, and Cohen[2] demonstrated that an increase in intraocular pressure could occur after intracapsular cataract extraction in eyes not receiving alpha-chymotrypsin.[2] Intraocular pressure increases have also been noted after extracapsular cataract extraction,[3,4] which are almost identical to those found after intracapsular cataract extraction.[5-8] We do not know the exact mechanism of this rise in intraocular pressure. It may be caused by either mechanical obstruction of the trabecular meshwork by zonular fragments, inflammation, or deformation of the angle structures. Recent studies have evaluated the intraocular pressure-lowering effects of timolol maleate, acetylcholine, carbachol, acetazolamide, and pilocarpine gel after both intracapsular and extracapsular cataract extraction.[3,4,9-11] Some of these pharmacologic agents have been shown to suppress intraocular pressure.

In previous studies measuring intraocular pressure increase after intracapsular cataract extraction, the measurements were not made within the first few postoperative hours. The effect of sodium hyaluronate was also not evaluated, even though many surgeons routinely use sodium hyaluronate when implanting posterior chamber intraocular lenses.

To our knowledge, there have been no reports on the incidence and magnitude of increased intraocular pressure in the immediate postoperative period in a series of eyes undergoing planned uncomplicated extracapsular cataract extraction by nucleus expression and phacoemulsification with posterior chamber intracapsular lens implantation. Herein we report our findings using these techniques, with and without the use of sodium hyaluronate, in an outpatient population.

Patients and Methods

We studied two surgeons' consecutive patients undergoing routine extracapsular cataract extraction with implantation of a posterior chamber lens over a five-month period. We excluded patients with preexisting glaucoma or those taking topical or systemic beta-blockers, corticosteroids, epinephrine, or carbonic anhydrase inhibitors. We obtained informed consent from all patients.

Tobramycin eyedrops were administered the night before surgery. Just before cataract surgery, we dilated the eyes with 1% tropicamide hydrochloride and 2.5% phenylephrine hydro-

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chloride. All patients received a modified Van Lint eyelid block and a retrobulbar injection of bupivacaine hydrochloride 0.75%, lidocaine 2%, and hyaluronidase. We applied digital massage for five minutes and did not use a Honan intraocular pressure reducer.

Extracapsular cataract extraction was performed by either nucleus expression through a 10- to 11-mm fornix-based incision or phacoemulsification through a 3.5-mm wound enlarged to about 7.0 mm. This allowed for the insertion of a posterior chamber intraocular lens. The type of cataract surgery performed was decided empirically based on the preoperative clinical appearance of the nucleus. We closed wounds with a combination of 8-0 Vicryl and 10-0 nylon sutures. Sodium hyaluronate was used only if the anterior chamber did not remain deeply formed during lens insertion. When sodium hyaluronate was used, it was aspirated and diluted at the end of the procedure. We did not routinely administer beta-blockers, cholinergic agents, or carbonic anhydrase inhibitors. A dexamethasone-neomycin combination ointment was applied to the eyes at the completion of surgery. We did not measure intraocular pressure at this time.

We obtained applanation intraocular pressure measurements within one week before surgery. We also measured intraocular pressure two to three hours and 24 hours after surgery. We took certain empiric precautions. If the intraocular pressure was greater than 30 mm Hg at two to three hours after surgery, we placed one drop of 0.5% betaxolol hydrochloride on the eye every 12 hours. If the intraocular pressure was greater than 40 mm Hg at two to three hours, the patient received one drop of topical 0.5% betaxolol hydrochloride and 500 mg of oral acetazolamide every 12 hours.

All patients were discharged after the first postoperative intraocular pressure measurement two to three hours after surgery. They returned for an examination 24 hours after surgery. At this time, we treated patients with topical corticosteroids, antibiotics, and intraocular pressure-lowering medications, as necessary. The results are reported as the mean ± 1 S.D. Student's and paired *t*-tests and chi-square analysis were used when appropriate.

Results

We studied 58 eyes (58 patients). There were 24 men and 34 women, with a mean age of 74 years. Surgery was performed on 32 right eyes and 26 left eyes. Of 58 eyes, 35 underwent cataract extraction by nucleus expression and 23 by phacoemulsification. The mean ultrasound time in the latter group was 1.9 ± 0.9 minutes.

Mean preoperative intraocular pressure was 17.8 ± 3.7 mm Hg. Mean postoperative intraocular pressure was 26.2 ± 9.8 mm Hg at two to three hours, 22.3 ± 9.5 mm Hg at 24 hours, and 16.9 ± 5.1 mm Hg at one week. At two to three hours, 34 eyes (59%) had an intraocular pressure equal to or greater than 25 mm Hg, 21 (36%) had a pressure equal to or greater than 30 mm Hg, and seven (12%) had a pressure equal to or greater than 40 mm Hg. Of those 21 patients with an intraocular pressure of 30 mm Hg or more at the two- to three-hour measurement, 13 (64%) had an intraocular pressure of at least 25 mm Hg at 24 hours, despite treatment with betaxolol hydrochloride 0.5%

We used sodium hyaluronate in 25 eyes. In this group, nine eyes (36%) had an intraocular pressure equal to or greater than 30 mm Hg at two to three hours. Of 35 eyes having cataracts removed by nucleus expression, 15 had an intraocular pressure equal to or greater than 30 mm Hg, whereas only six of 23 eyes (27%) undergoing phacoemulsification reached this level. An equal number of eyes in the group that did and the group that did not receive sodium hyaluronate reached an intraocular pressure of 30 mm Hg at two to three hours. Mean intraocular pressure in these eyes was still increased one day after surgery.

Surgical technique was evaluated as a factor influencing intraocular pressure (Table). The mean intraocular pressures at the two- to three-hour measurement in eyes that underwent nucleus expression were similar, regardless of whether sodium hyaluronate was used. We found the same results with phacoemulsification; however, only a small number of eyes in this group received sodium hyaluronate.

Discussion

This study demonstrates that a significant number of nonglaucomatous eyes undergoing extracapsular cataract surgery have an acute rise in intraocular pressure. Despite the various surgical techniques used, the percentage of eyes in this study with increased intraocular

TABLE
INFLUENCE OF SURGICAL TECHNIQUE ON INTRAOCULAR PRESSURE

	MEAN ± S.D. INTRAOCULAR PRESSURE (MM HG)							
TIME OF MEASUREMENT	ALL EYES (N = 58)	NUCLEUS EXPRESSION (N = 35)	PHACOEMULSIFICATION (N = 23)	SODIUM HYALURONATE (N = 25)	NUCLEUS EXPRESSION WITHOUT SODIUM HYALURONATE (N = 16)	PHACOEMULSIFICATION WITHOUT SODIUM HYALURONATE (N = 17)	NUCLEUS EXPRESSION WITH SODIUM HYALURONATE (N = 19)	PHACOEMULSIFICATION WITH SODIUM HYALURONATE (N = 6)
Preoperative	17.8 ± 3.7	17.9 ± 4.3	17.2 ± 2.1	18.9 ± 4.5	16.1 ± 3.15	17.3 ± 0.9	19.2 ± 4.8	16.8 ± 3.9
2 to 3 hrs Postoperative	26.2 ± 9.8	27.4 ± 10.0	24.2 ± 9.1	25.6 ± 9.5	28.6 ± 10.4	24.8 ± 9.4	26.5 ± 9.8	22.7 ± 8.8
24 hrs Postoperative	22.3 ± 9.5	22.2 ± 10.8	22.3 ± 7.5	22.9 ± 9.7	19.7 ± 12.1	24.0 ± 5.5	24.5 ± 9.1	18.2 ± 11.0

pressure is similar to the results reported previously after both intracapsular and extracapsular surgery.[1-4,9-11] Rich, Radtke, and Cohen[2] performed hourly intraocular pressure measurements after intracapsular cataract surgery. They found the highest mean intraocular pressure occurring between six and eight hours. We only measured intraocular pressures at two to three hours after surgery because we needed to discharge our outpatients. We may have found higher intraocular pressures if we could have repeated the intraocular pressure measurements. This intraocular pressure increase is important because some eyes may be susceptible to moderate transient increases in intraocular pressure (for example, eyes with advanced glaucoma or anterior ischemic optic neuropathy).[12,13] Relatively brief intraocular pressure increase has also caused visual dysfunction after anterior segment laser surgery in both glaucomatous and nonglaucomatous eyes.

We found a statistically significant difference in mean intraocular pressures at two to three hours between eyes that underwent nucleus expression and those that underwent phacoemulsification. This did not relate to the use of sodium hyaluronate. At 24 hours, however, the mean intraocular pressures for these groups were almost identical. We cannot explain this difference, and we are not certain of the clinical relevance of this finding.

The mechanism for the intraocular pressure increase was not investigated in our study. It may be similar to that described for intracapsular cataract extraction.[5-8] Although there are no zonular fragments dispersed during extracapsular cataract extraction, pigment is liberated. High- and low-molecular-weight proteins are liberated by the manipulation of the iris during nucleus expression, irrigation, and intraocular lens insertion. This may obstruct the outflow pathways and lead to increases in intraocular pressure. The use of fine sutures, stepped incisions, and meticulous closure under high magnification may contribute to this intraocular pressure increase by producing a water-tight closure.

Sodium hyaluronate, when left in the anterior chamber, can increase intraocular pressure.[13,14] However, we removed most sodium hyaluronate with anterior chamber irrigation before wound closure. The intraocular pressure spike caused by sodium hyaluronate may have been altered by the intraocular pressure spike caused by cataract surgery.

Our study, like previously reported studies, did not measure intraocular pressure at the termination of cataract surgery. Hyperinflation of the globe at the end of the procedure may have, in part, contributed to the degree of intraocular pressure increase. The role of this factor has not yet been evaluated in this intraocular pressure rise.

The relatively high incidence of intraocular pressure increase occurring in the immediate postoperative period after extracapsular cataract extraction with posterior chamber lenses is of note. This complication can easily go unnoticed until the first postoperative visit, since cataract surgery is routinely done in an outpatient setting. Visual damage from transient increases of intraocular pressure could be devastating and reduce the benefit of cataract extraction.[12,13] The prophylactic use of intraocular pressure-lowering agents[3,4,9-11] should be routinely used. It may also be prudent to measure the intraocular pressure of patients at risk of optic nerve damage before discharge.

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OPHTHALMIC MINIATURE

He began slowly to follow Welch, his heart starting to pound and mist breaking out on his spectacles. He allowed a terrible grimace to dawn on his features, forcing his chin down as far as possible and trying to bring his nose up between his eyes. When this was nearing completion, he took off his glasses to rub them clear.

Kingsley Amis, *Lucky Jim*
New York, Viking Penguin Inc., 1953, p. 179

Photocoagulation Treatment of Radiation Retinopathy

James L. Kinyoun, M.D., Mark E. Chittum, M.D., and Craig G. Wells, M.D.

We studied the visual and anatomic effects of focal photocoagulation for clinically significant radiation macular edema in five eyes of four patients and panretinal photocoagulation for proliferative radiation retinopathy in six eyes of three patients. Focal and limited scatter photocoagulation was successful in preventing further vision loss in all five eyes treated for macular edema. Three eyes treated with panretinal photocoagulation had regression of neovascularization. The other three eyes treated for proliferative retinopathy subsequently had dense vitreous hemorrhages that required vitrectomy for restoration of useful vision.

RADIATION RETINOPATHY is an occlusive microangiopathy that is manifest by one or more of the following: retinal hemorrhages, cotton-wool spots, microaneurysms, telangiectatic vessels, macular edema, exudates, neovascularization of the disk or retina, vitreous hemorrhage, optic atrophy, rubeosis iridis, and neovascular glaucoma. Radiation retinopathy can occur after radioactive plaque or external beam irradiation for ocular and orbital tumors, Graves' ophthalmopathy, and intracranial lesions not adjacent to the eye.[1-3] Although the clinical manifestations of radiation retinopathy have been well defined, published information is scarce regarding treatment of this potentially blinding complication.[2,4,5]

We studied the visual and anatomic effects of photocoagulation treatment in nine eyes of five patients with radiation retinopathy. Treatment indications and techniques were based on published results of photocoagulation treatment for diabetic retinopathy,[6,7] a disease with similar pathophysiology.[8] Details of the radiation treatment and early radiation retinopathy findings in Cases 1 through 3 have been published previously.[2] This serious treatment complication in all three of these cases was probably caused by errors in radiotherapy technique and dosage calculations. Careful review of records indicates that in each of these three cases the patient received approximately twice the reported total dosage of 2,000 rad. None of our patients had diabetes mellitus or other vascular diseases that might be confused with radiation retinopathy.

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Case Reports

Case 1

A 28-year-old man with Graves' ophthalmopathy was treated with external beam irradiation in 1978. A reported total of 2,000 rad was applied to each orbit in ten fractions over a two-week period.

One year later, visual acuity was R.E.: 20/25 and L.E.: 20/40. Based on characteristic retinal and optic nerve findings, a diagnosis of radiation retinopathy and optic neuropathy was made. Over the next three years, he developed neovascularization of the disk and retina with preretinal and vitreous hemorrhages in both eyes.

Panretinal argon laser photocoagulation was applied to each eye (Table 1). Between the major vascular arcades and vortex ampullae 500-μm, 0.1-second burns spaced two burn diameters apart were scattered. Power settings were adjusted to achieve moderately white lesions. Spacing between burns was decreased to treat confluently the base of elevated new vessels with fibrosis inferior to the left optic nerve.

The neovascularization regressed bilaterally and the vitreous hemorrhages spontaneously cleared. In 1985, however, a recurrent vitreous hemorrhage occurred in the left eye, which was caused by vitreoretinal traction at the site of elevated fibrovascular proliferation. The hemorrhage failed to clear, and a pars plana vitrectomy was performed (Table 2).

TABLE 1
PANRETINAL PHOTOCOAGULATION FOR PROLIFERATIVE RADIATION RETINOPATHY*

CASE NO.	EYE	INITIAL VISUAL ACUITY†	FUNDUS FINDINGS	VITREOUS HEMORRHAGE‡	NO. OF TREATMENT BURNS (SESSIONS)	FINAL VISUAL ACUITY†	FOLLOW-UP (MOS)
1	R.E.	20/100	NVD	+	702 (3)	20/70	66
	L.E.	20/200	NVD, NVE	+	631 (2)	C.F.	62
3	R.E.	C.F.	NVE	+	1135 (3)	20/200	24
	L.E.	20/400	NVE	+	1361 (4)	H.M.	23
4	R.E.	20/50	NVD, NVE	+	1330 (2)	20/100	19
	L.E.	20/40	NVD, NVE, TRD	+	1200 (2)	20/80	19

*NVD, new vessels on disk; NVE, new vessels elsewhere; TRD, traction retinal detachment.
† C.F., counting fingers; H.M., hand motion.
‡+ indicates present.

Postoperatively, the patient's visual acuity was 20/70 in the right eye and counting fingers in the left eye. The right eye had optic disk pallor and retinal thickening less than 1 disk diameter in size and greater than 500 μm from the center of the macula. The fluorescein angiogram showed capillary nonperfusion in the papillomacular bundle with enlargement of the capillary-free zone (Fig. 1). Decreased visual acuity was attributed to radiation optic neuropathy and macular ischemia.

The left disk was also pale and the macula was diffusely thickened. An incomplete circinate ring of exudates was centered temporal to the macula and cystoid edema was present (Fig. 2, left). Fluorescein angiography showed widespread capillary nonperfusion and leakage from microaneurysms (Fig. 2, right).

Argon green laser photocoagulation was applied to areas of capillary nonperfusion and leaking microaneurysms judged to be responsible for the clinically significant macular edema in the left eye. Burns of 50 and 100 μm with power settings of 100 to 250 mW and duration of 0.1 second were used. Acceptable end points were darkening or whitening of microaneurysms, which often required several burn applications. Moderately white burns, spaced one burn diameter apart, were scattered throughout areas of capillary nonperfusion (Table 3).

Six months later, the visual acuity was still 20/70 in the right eye and counting fingers in the left eye. Macular thickening and exudates decreased but cystoid edema remained centrally in the left eye.

Case 2

A 50-year-old man with Graves' ophthalmopathy was treated with external beam irradiation in 1979. The reported total dose to each orbit was 2,000 rad given in ten fractions over a two-week period. Nine months later, radiation retinopathy was diagnosed in both eyes.

In 1983, visual acuity was 20/25 in the right eye but had decreased to only light perception in the left eye because of vitreous hemorrhage and posterior subcapsular cataract. Lensectomy and vitrectomy procedures were performed

TABLE 2
PARS PLANA VITRECTOMY FOR NONCLEARING VITREOUS HEMORRHAGE CAUSED BY PROLIFERATIVE RADIATION RETINOPATHY*

CASE NO.	EYE	PREVITRECTOMY VISUAL ACUITY	POSTVITRECTOMY VISUAL ACUITY	RECURRENCE OF NEOVASCULARIZATION OR HEMORRHAGE	FOLLOW-UP (MOS)
1	L.E.	C.F.	C.F.	No	7
2	L.E.	H.M.	20/400	No	48
4	L.E.	H.M.	20/80	No	12

*C.F., counting fingers; H.M., hand motion.

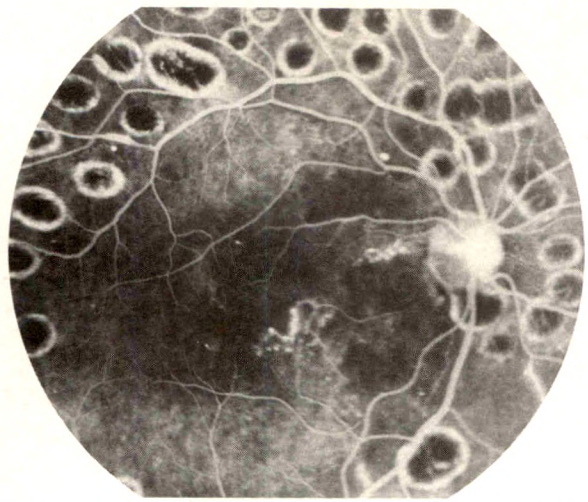


Fig. 1 (Kinyoun, Chittum, and Wells). Case 1, right eye. Late venous phase of angiogram shows capillary nonperfusion in papillomacular bundle and enlargement of capillary-free zone. Early leakage from microaneurysms is present inferonasal to center of the macula.

in the left eye but postoperative visual acuity improved to only 20/400 in the left eye because of macular edema and ischemia (Fig. 3).

In August 1986, visual acuity in the right eye had decreased to 20/40. Exudates and retinal thickening were present within 500 μm of the center of the macula. During two treatment sessions, focal and limited scatter argon green laser photocoagulation was applied to microaneurysms and areas of diffuse leakage as identified in the fluorescein angiogram (Fig. 4, left). The treatment technique was the same as that used in Case 1 except that the limited scatter treatment used in Case 2 was applied to areas of diffuse leakage, whereas in Case 1 the scatter burns were applied to areas of capillary nonperfusion.

Postoperative visual acuity improved to 20/20 in the right eye (Table 3). Only a few exudates remain temporal to the macula and the retina is no longer thickened (Fig. 4, right).

Case 3

In 1979, a 40-year-old woman with Graves' ophthalmopathy was treated with a reported total of 2,000 rad to each posterior orbit. Two months after treatment the patient complained of decreased vision in both eyes, and ophthalmoscopic examination disclosed characteristic fundus findings of radiation retinopathy. The patient later developed corneal opacification and cataract in both eyes. The right eye was treated with penetrating keratoplasty, extracapsular cataract extraction, and posterior chamber lens implantation.

In 1985, she had new vessels elsewhere and vitreous hemorrhage in both eyes. Both eyes were treated with panretinal argon photocoagulation (Table 1). The panretinal technique was similar to that used in Case 1. Burns were not placed closer than 500 μm from the nasal disk

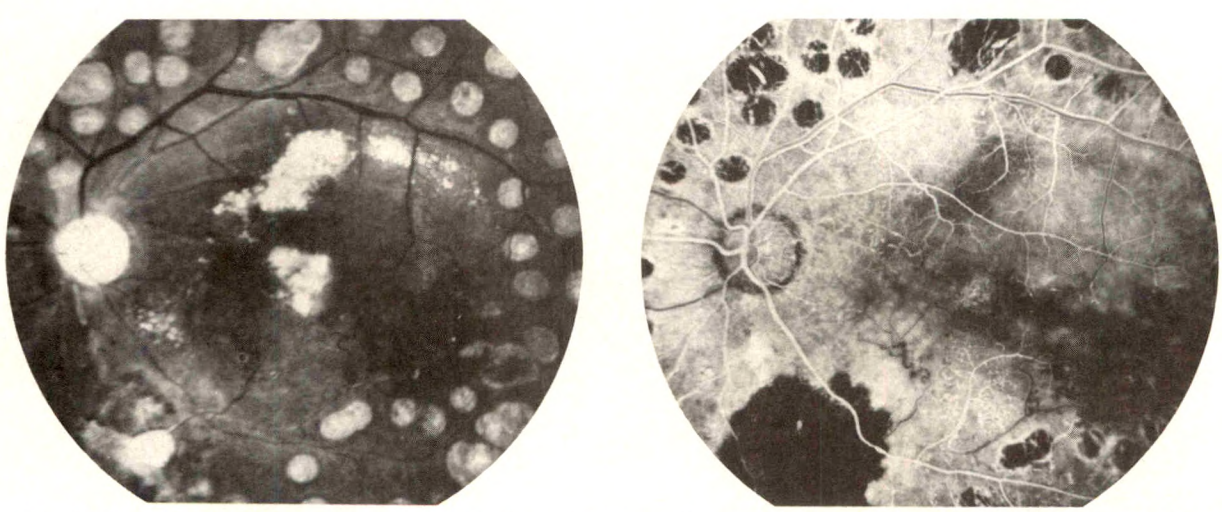


Fig. 2 (Kinyoun, Chittum, and Wells). Left, Case 1, left eye. Incomplete circinate ring is centered temporal to macula with exudates in superior and central macula. Optic disk is pale, and large hemorrhages and microaneurysms are located temporally. Right, Early venous phase of angiogram shows widespread capillary nonperfusion throughout posterior retina with hyperfluorescence of abnormal capillaries and microaneurysms.

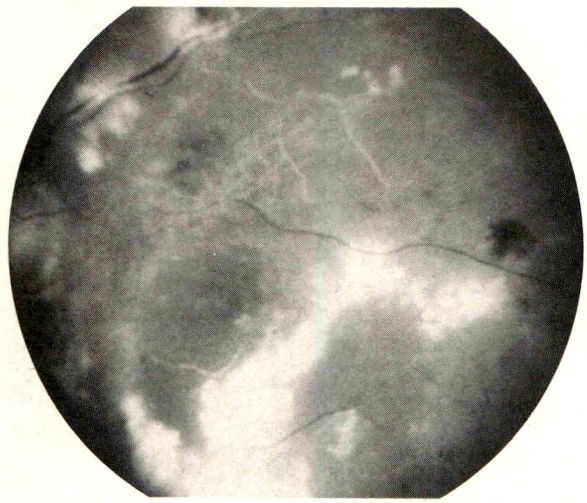


Fig. 3 (Kinyoun, Chittum, and Wells). Case 2, left eye. Macular edema and ischemia manifested by exudates and vascular sheathing (white opacification of vessel walls).

margin or closer than two disk diameters temporal, superior, and inferior to the center of the macula.

Two years later, visual acuity was 20/200 in the right eye and hand motion in the left eye. The neovascularization regressed and the vitreous hemorrhage cleared in the right eye but a dense vitreous hemorrhage was present in the left eye. The poor visual acuity in the right eye was attributed to radiation optic neuropathy.

Case 4

A 28-year-old woman had a left frontotemporal oligodendroglioma resected in 1981. In 1983, tumor recurrence was treated with external beam irradiation totaling 4,500 rad to a wide field with a 6,000-rad boost to a reduced field.

In March 1983, the patient had decreased visual acuity (R.E.: 20/50 and L.E.: 20/40) and fundus findings typical of radiation retinopathy. Blood glucose levels were normal. Eleven months later, she had developed new vessels on the disk and elsewhere with vitreous hemorrhage in both eyes (Fig. 5). Both eyes were treated with argon laser panretinal photocoagulation. Treatment technique was similar to that used in Cases 1 and 3 (Table 1).

The neovascularization regressed in the right eye, but the left eye later had a dense vitreous hemorrhage that decreased visual acuity to hand motion. B-scan ultrasonography disclosed an extramacular traction retinal detachment superior to the optic nerve. The hemorrhage did not clear over the following seven months and a pars plana vitrectomy was performed. Postoperative visual acuity was 20/80 in the left eye (Table 2).

Visual acuity in the right eye later decreased

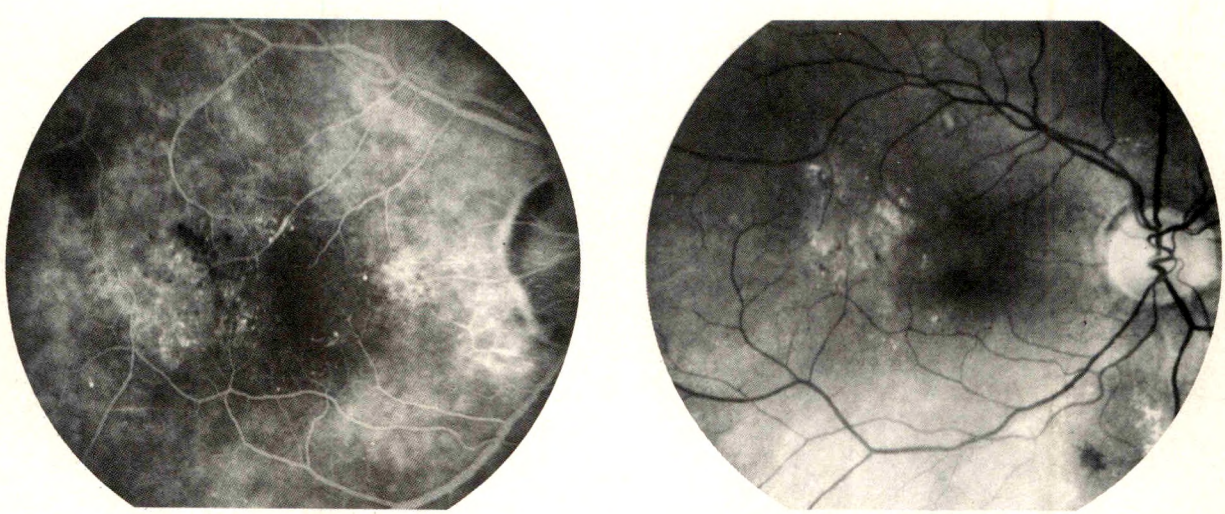


Fig. 4 (Kinyoun, Chittum, and Wells). Left, Case 2, right eye. Late venous phase of angiogram shows hyperfluorescent microaneurysms surrounding the center of macula with leakage temporally. Right, Fourteen months after initial treatment, the retina is no longer thickened and only a few exudates remain temporal to the macula (microaneurysms with exudates inferior to optic nerve are greater than two disk diameters from center of macula and were not treated).

TABLE 3
ARGON GREEN LASER PHOTOCOAGULATION FOR CLINICALLY SIGNIFICANT RADIATION MACULAR EDEMA*

CASE NO.	EYE	PRETREATMENT VISUAL ACUITY	NUMBER OF TREATMENT BURNS (SESSIONS)	POSTTREATMENT VISUAL ACUITY	FOLLOW-UP (MOS)
1	L.E.	C.F.	284 (2)	C.F.	6
2	R.E.	20/40	149 (2)	20/20	14
4	R.E.	20/100	171 (1)	20/80	3
5	R.E.	20/50	295 (4)	20/25	14
	L.E.	20/400	349 (2)	20/80	22

*C.F., counting fingers.

to 20/100 because of cystoid macular edema involving the center of the macula (Fig. 6, left). Limited scatter treatment and focal burns (Table 3) were applied to diffuse areas of leakage and leaking microaneurysms, respectively (Fig. 6, right). Three months later, visual acuity had improved to 20/80 in the right eye. Retinal edema had decreased but cystoid spaces remained in the center of the macula.

Case 5

A 61-year-old man with Graves' ophthalmopathy was reportedly treated with 2,000 rad of external beam irradiation to each orbit. Six years later, visual acuity had decreased to 20/400 in the left eye. Ophthalmic examination disclosed retinal findings consistent with radiation retinopathy in both eyes.

In January 1986, visual acuity was R.E.: 20/50 and L.E.: 20/400. There was no afferent pupillary defect but retinal thickening was present in the center of both maculas with cystoid edema in the left eye (Figs. 7, top left and 8, top left). Fluorescein angiography disclosed an enlarged capillary-free zone in each eye as well as capillary nonperfusion and late leakage from microaneurysms and microvascular abnormalities (Figs. 7, top right and 8, top right).

The clinically significant radiation macular edema in both eyes was treated with argon green photocoagulation. The same focal technique used in Case 1 was used during four treatment sessions of the right eye and two treatment sessions of the left eye. The macular edema resolved in both eyes (Figs. 7, bottom left and 8, bottom left) and visual acuity improved to 20/25 in the right eye and 20/80 in the left eye (Table 3).

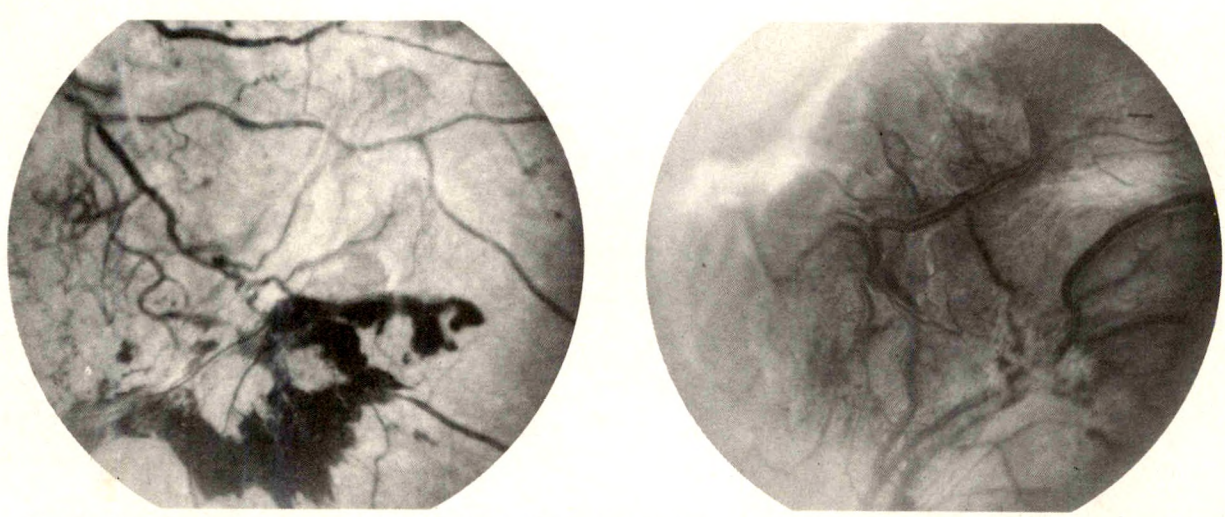


Fig. 5 (Kinyoun, Chittum, and Wells). Left, Case 4, right eye. Neovascularization with preretinal blood is present inferonasal to optic nerve. Right, Left eye. Fibrovascular proliferation with preretinal and vitreous blood is located superior to optic nerve.

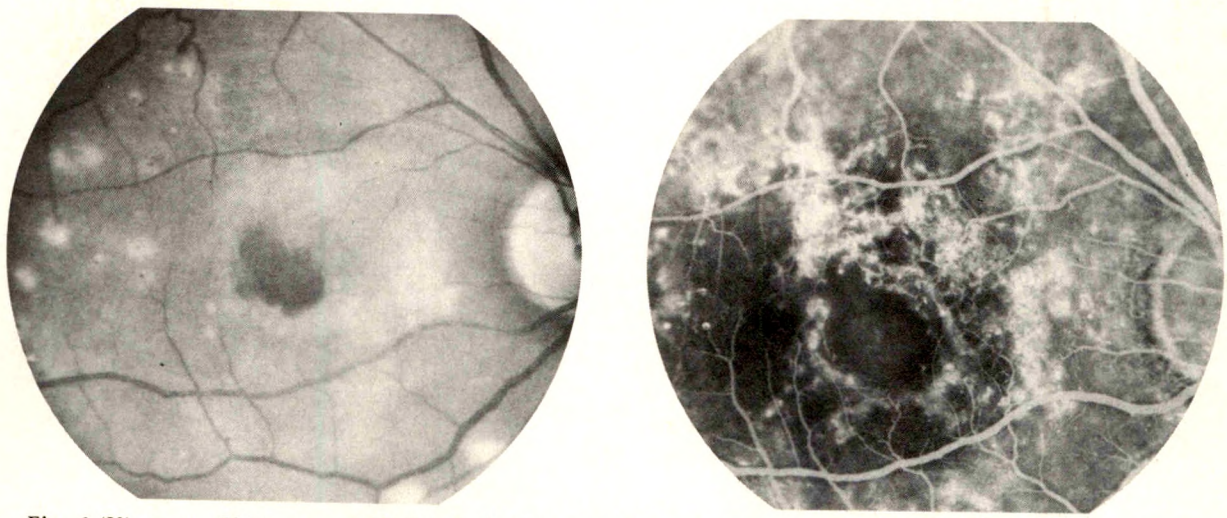


Fig. 6 (Kinyoun, Chittum, and Wells). Left, Case 4, right eye. Large cyst is present in center of macula and fresh laser burns are scattered throughout area of retinal thickening but not closer than 500 μm from center of capillary-free zone. Right, Enlarged capillary-free zone and adjacent areas of focal and diffuse leakage can be seen during venous phase of angiogram. Leakage into small cystoid spaces is present in papillomacular bundle.

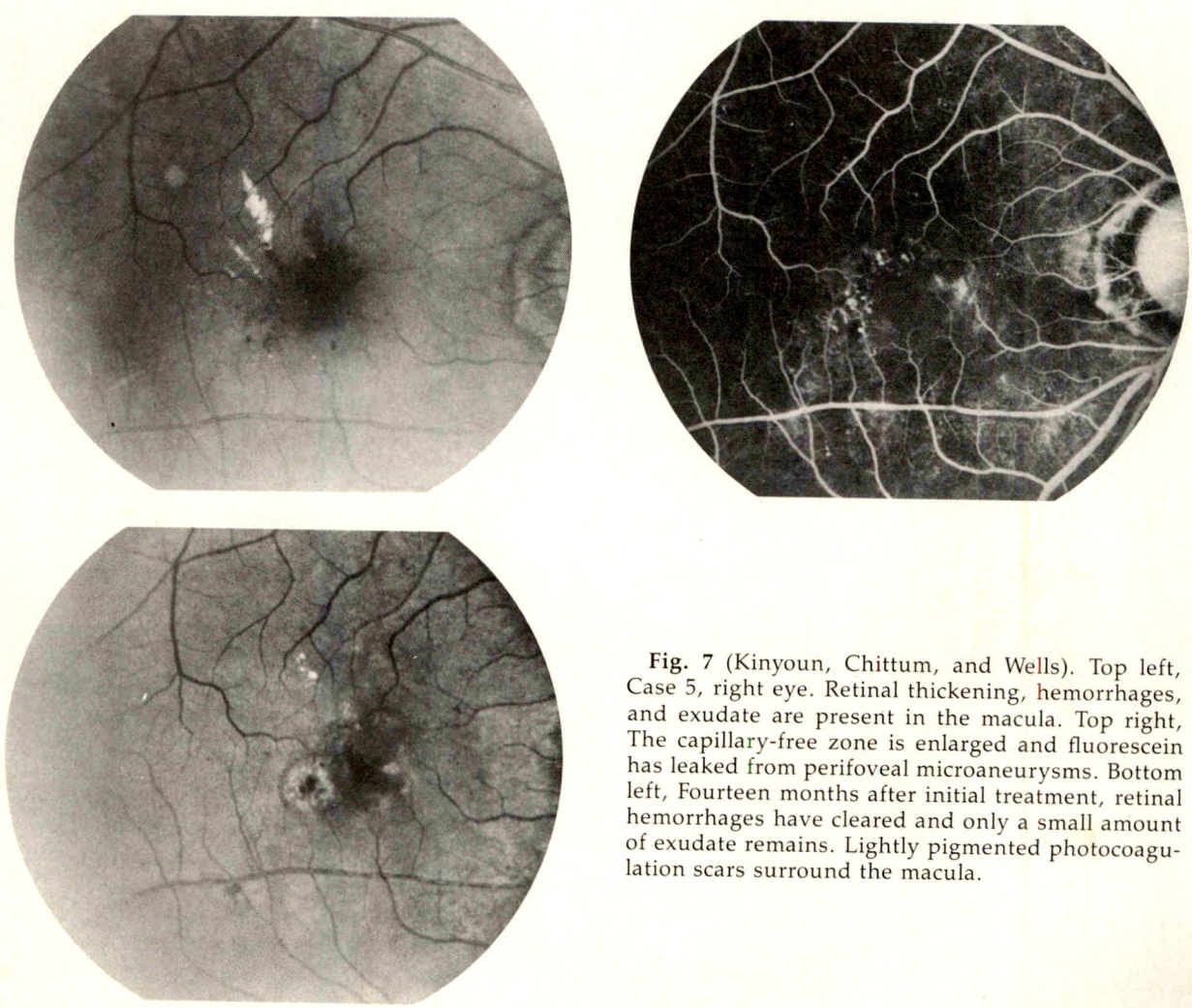


Fig. 7 (Kinyoun, Chittum, and Wells). Top left, Case 5, right eye. Retinal thickening, hemorrhages, and exudate are present in the macula. Top right, The capillary-free zone is enlarged and fluorescein has leaked from perifoveal microaneurysms. Bottom left, Fourteen months after initial treatment, retinal hemorrhages have cleared and only a small amount of exudate remains. Lightly pigmented photocoagulation scars surround the macula.

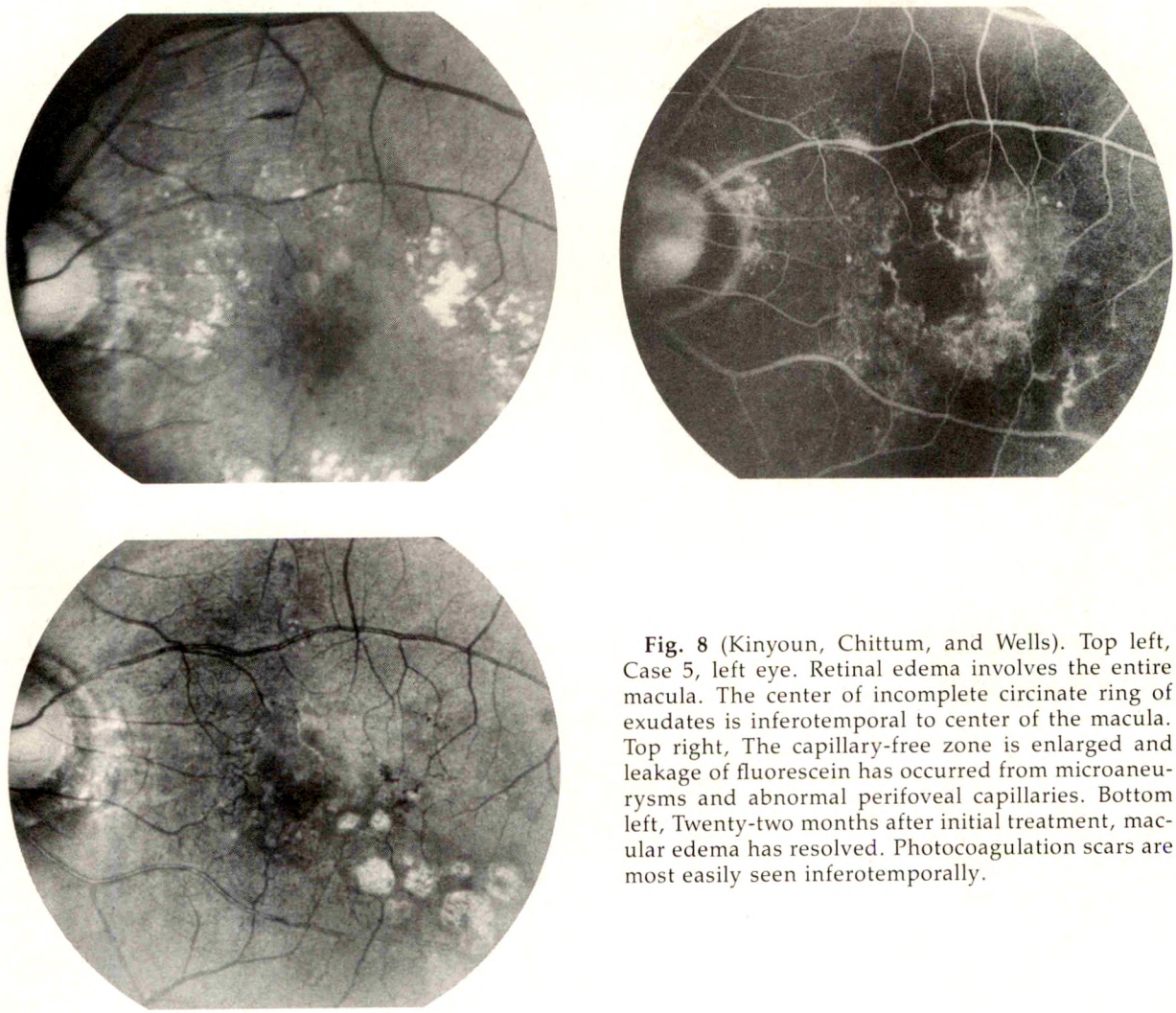


Fig. 8 (Kinyoun, Chittum, and Wells). Top left, Case 5, left eye. Retinal edema involves the entire macula. The center of incomplete circinate ring of exudates is inferotemporal to center of the macula. Top right, The capillary-free zone is enlarged and leakage of fluorescein has occurred from microaneurysms and abnormal perifoveal capillaries. Bottom left, Twenty-two months after initial treatment, macular edema has resolved. Photocoagulation scars are most easily seen inferotemporally.

Discussion

Inflammation and degeneration of the retina as a consequence of roentgen and radium rays were described as early as 1933.[9] Other adverse effects have included cataract,[10] diffuse atrophy of the retinal pigment epithelium,[5] choroidal infarcts,[11] and radiation optic neuropathy (presumably secondary to radiation-induced vasculopathy of the optic nerve).[12] Severely ischemic globes may develop rubeosis iridis and neovascular glaucoma, which results in loss of vision and the eye.

Fluorescein angiograms of eyes with radiation retinopathy typically show dilated and tortuous macular vessels with aneurysmal and saccular dilatation.[13] Leakage occurs from these intraretinal microvascular abnormalities as well as from disk and retinal neovascularization. The leakage may be severe enough to cause clinically detectable retinal thickening with or without cystoid edema as seen in four of our cases. Capillary nonperfusion is consistently seen, and occasional large retinal vessels may also be occluded. A less specific finding is transmission hyperfluorescence corresponding to areas of retinal pigment epithelial atrophy.

The occurrence of retinopathy is related not only to the total dose received but also to the daily fraction size.[14] Over 3,000 rad is usually necessary to cause retinopathy,[15] though it has been described in patients who received 1,500 rad.[16] Daily dose fractionation in excess of 200 rad is associated with an increased incidence of radiation retinopathy and optic neuropathy.[17]

Our patients received a reported 2,000 to 6,000 total rad over two- to seven-week periods. Daily fraction sizes ranged from 180 to 200 rad. Patients with preexisting vascular disease (for example, diabetes mellitus and collagen vascular disease) or previous chemotherapy are susceptible to developing retinopathy at lower doses of radiation,[1] but this was not a factor in our cases.

External beam radiation appears to affect mainly the inner layers of the retina; the photoreceptors are relatively resistant. Irvine and associates[8] reported the histopathology of radiation retinopathy in monkeys treated with external beam irradiation. Clinically, these animals developed retinopathy within ten to 20 months after treatment. Histologic studies showed loss of endothelial cells, disruption of pericytes, capillary closure, and intraretinal microvascular abnormalities that parallel the histopathologic changes seen in diabetic retinopathy.

Radiation retinopathy in humans usually develops within three months to three years after treatment. Initial complaints include blurred vision or floaters, or both, caused by macular edema or ischemia, vitreous hemorrhage, cataract, optic neuropathy, rubeotic glaucoma, or traction retinal detachment. These causes of vision loss are also seen in patients with diabetic retinopathy. Since radiation retinopathy and diabetic retinopathy are clinically and histopathologically similar, it seems reasonable to base treatment of radiation retinopathy on well-established guidelines for treatment of diabetic retinopathy.[6,7]

Seven eyes in four of our patients developed neovascularization that was classified as high-risk for severe visual loss[6] because of complications of radiation rather than diabetes mellitus. A dense vitreous hemorrhage prevented treatment of one eye. Scatter (for new vessels on the disk) and confluent local (for new vessels elsewhere) photocoagulation was applied with the argon blue-green laser. Burns of 500 μm of 0.1-second duration with power settings to achieve an end point of mild to moderate retinal whitening were used. The intensity of these burns is less than that used by us to treat proliferative diabetic retinopathy. Also, fewer burns (702 to 1,361) were used and spaced farther apart than for scatter treatment of proliferative diabetic retinopathy.[18] Since these patients had preexisting optic disk pallor, we reasoned that less intense and fewer photocoagulation burns might minimize subsequent optic atrophy. Three treated eyes had regression of new vessels without recurrent vitreous hemorrhages over follow-up periods of 19 to 66 months. The other three eyes subsequently had dense, nonclearing vitreous hemorrhages.

Pars plana vitrectomy was performed in three eyes with nonclearing vitreous hemorrhages. Vitreous traction to sites of fibrovascular proliferation with localized traction retinal detachment was present in each eye. Postoperative vision improved in each eye but was limited by radiation macular edema and ischemia as well as radiation optic neuropathy. None of the patients have had a recurrence of vitreous hemorrhage or regrowth of new vessels.

Five eyes were classified as having clinically significant macular edema,[7] again because of complications of radiation rather than diabetes mellitus. Argon green laser burns (0.05 to 0.1 second) were used to treat these eyes. Microaneurysms and other focal sites of leakage as identified in the fluorescein angiogram were treated with 50- and 100-μm burns. Areas of diffuse leakage and capillary nonperfusion associated with macular edema and within two disk diameters of the center of the macula were photocoagulated with a grid pattern of 50- or 100-μm burns, each burn separated by one burn diameter.[19] This treatment has been effective in preventing further vision loss in all five eyes and has resulted in two or more lines of improved vision in three eyes over follow-up periods ranging from three to 22 months (Table 3).

We believe the results in these five patients support the use of photocoagulation treatment for selected eyes with radiation retinopathy. Eyes with one or more high-risk characteristics,[6] clinically significant macular edema,[7] or both, should be considered for treatment with photocoagulation. Our experience suggests that eyes with radiation retinopathy respond as well to photocoagulation as eyes with diabetic retinopathy. Also, nonclearing vitreous hemorrhage caused by radiation retinopathy can be safely managed with pars plana vitrectomy techniques.

We agree that radiation maculopathy and neovascularization will occur in an almost predictable fashion.[20] With the increased use of radiation for treatment of ocular and orbital disease, these complications will become more common, and finding effective treatment modalities will be even more imperative. Until a well-controlled, randomized clinical trial is performed, we recommend applying the proven

indications and techniques for photocoagulation treatment of diabetic retinopathy to treatment of radiation retinopathy.

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OPHTHALMIC MINIATURE

Patrick Prentiss had come to think of his reading glasses as his "Irish spectacles," although he had purchased them, two years before, from an oculist in Paris. He did not require them for ordinary reading, save for the occasional footnote, but for the purposes of his present research they were a necessity. After a few hours at work on old newspaper files, the reports of trials, of special and select committees, the print, wretched at best, would begin to waver and recede, diminishing.

Thomas Flanagan, *The Tenants of Time*
New York, E. P. Dutton, 1988, p. 227

New Contact Lens for Observation and Coagulation of the Retina and Choroid

Pascal Rol, Opt. Eng., Franz Fankhauser, M.D., and Sylwia Kwasniewska, M.D.

The optical performance of a new contact lens for observation and irradiation of the retina and choroid represents a compromise between Goldmann's contact lens and a wide-angle system in regard to magnification, resolution, and size of the field of view.

BOTH OBSERVATION and photocoagulation of the retina and choroid are fundamental tasks in ophthalmology. Goldmann[1] developed a contact lens, with or without internal mirrors, for observation of the fundus oculi. By using the mirrors, the entire retina may be examined. In the normal phakic eye, however, the ora serrata can only be viewed indirectly by scleral indentation. Many variations of this contact lens are in use today.[2]

More recently, other contact lenses have been developed. Their clinical indications are generally the same as the Goldmann lens, but their design is based on different optical principles. One such lens is the Panfunduscope,[3] which evolved from the El Bayadi lens.[4,5] When compared with the Goldmann lens, the Panfunduscope provides a large field of view of the fundus, including the ora serrata. However, such a wide field of view is obtained at the expense of optical quality.

In many ways, these two types of contact lenses attempt to solve two different optical tasks. The contact lens to be described here, the CGR 3 lens, is oriented toward an optimization of the positive aspects of both optical principles.

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From the Institute for Biomedical Engineering, Zürich (Mr. Rol) and the University Eye Clinic (Drs. Fankhauser and Kwasniewska), Bern, Switzerland. This study was supported in part by the Swiss Commission for the Promotion of Scientific Research and Alcon Laboratories.

Reprint requests to Prof. Dr. F. Fankhauser, University Eye Clinic, 3010 Bern, Switzerland.

Goldmann Lens

The Goldmann lens (Fig. 1) is a negative lens of −64 diopters that forms an upright image (side-inverted when mirrors are used). It provides comfortable image magnification and also good image definition of the retina. The image thus obtained is sufficient for most diagnostic purposes. However, a relatively small field of view is available, forcing the observer into an iterative observation strategy when more than one restricted area of retina has to be examined. This may be time consuming when a large portion of the retina must be examined. Additionally, details may escape the attention of the observer and one or several retinal areas that should be inspected may be omitted. The observer must also spatially correlate the areas that have been examined in order to create a view of the whole. This may be particularly difficult if a disease process is present.

Panfunduscope

The Panfunduscope (Fig. 2), in contrast, is free of this constraint. The Panfunduscope provides the slit lamp with a real inverted intermediate image, somewhat like the indirect ophthalmoscope. The use of a sphere as a field lens results in a large field of view. This advantage, however, is obtained at the expense of visuali-

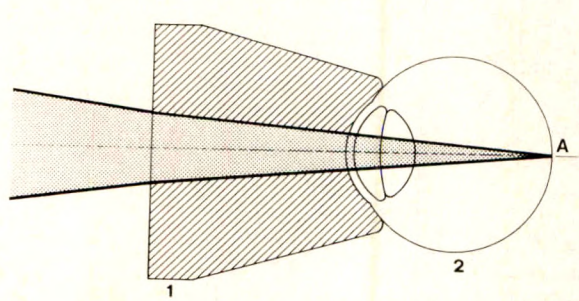


Fig. 1 (Rol, Fankhauser, and Kwasniewska). Diagram showing the optical path through the Goldmann lens. 1, Goldmann lens; 2, human eye; A, focus point on the retina.

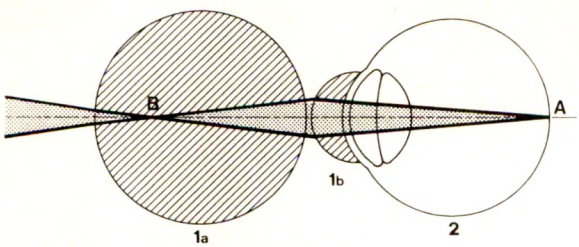


Fig. 2 (Rol, Fankhauser, and Kwasniewska). Diagram showing the optical path through the Panfunduscope. 1, Panfunduscope (a, focusing lens; b, field lens); 2, human eye; A, focus point on the retina; B, intermediate focus point (real intermediate image of the retina).

zation of details and image quality, particularly in the periphery. These disadvantages are the result of field curvature, which reduces resolution.

Laser Treatment

The same basic principles that are important for observation are also important in the treatment of the retina and the choroid with lasers using thermal energy transfer mechanisms, such as the argon ion laser.

When using the Goldmann lens, because of its plane entrance surface, the cone angle of the laser beam is reduced from 6 degrees (which is a typical value for an argon laser) to 4.1 degrees. This results in a focal spot diameter of 55 μm on the retina for a laser beam having a spot size of 50 μm in air. Enlargement of the laser spot to about 1 mm is possible in most systems by defocusing, that is, shifting the slit lamp forward by 8.5 mm. Consequently, the focus spot is shifted forward by 13.1 mm, resulting in a laser beam diameter of 2.16 mm on the posterior face of the crystalline lens (Fig. 3, top). This does not represent any risk to tissues anterior to the retina because the laser beam diameter is greater there than on the retina. The most important optical parameters related to the Goldmann lens are compiled in the Table. The values serve as a basis for evaluating other contact lenses for the retina. The weakest point is the small field of view, ±23 degrees (value calculated from nodal point of the eye).

When using the Panfunduscope, along with image size reduction, the focal spot diameter of the laser beam is enlarged by a factor of 1.3 as compared to the Goldmann lens and the cone angle is reduced from 6 to 3.45 degrees. The presence of an intermediate focus point (Fig. 2)

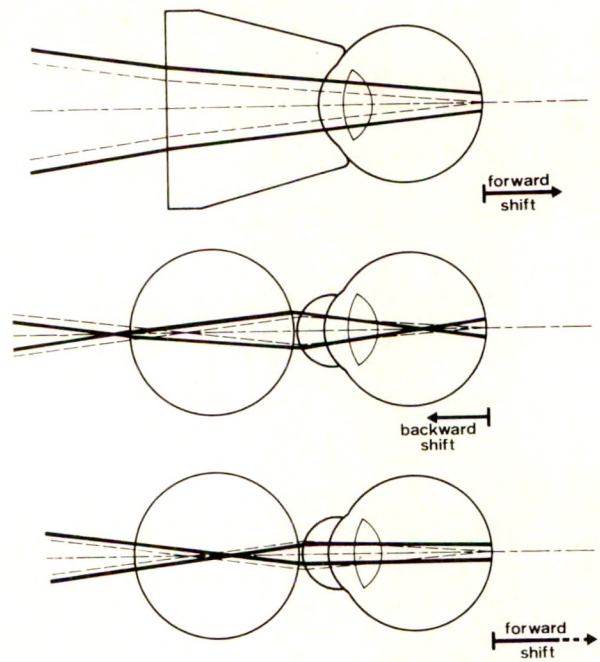


Fig. 3 (Rol, Fankhauser, and Kwasniewska). Shift of the laser beam to obtain a spot diameter on the retina of about 1 mm with the Goldmann lens (top), and with the Panfunduscope (middle and bottom). The dotted line represents the initial location of the beam to obtain the smallest spot size on the retina. The arrow indicates the direction of the shift.

within the contact lens may damage the latter when high energy or power densities are used. The narrow cone angle of the laser beam may also endanger the crystalline lens,[6] particularly when lenticular opacities exist.

The threat to the crystalline lens is particularly great when an enlargement of the laser spot to about 1 mm is anticipated. When the slit lamp is shifted, the crystalline lens may be affected in one of two ways. Either the slit lamp is shifted backward (Fig. 3, middle) by 7.0 mm, resulting in a shift of the focus point by 10.0 mm and a laser beam diameter of 0.67 mm on the posterior face of the crystalline lens, or the slit lamp is shifted forward (Fig. 3, bottom) by 6.5 mm, resulting in a shift of the focus point by 47 mm and a laser beam diameter of 1.29 mm on the posterior face of the crystalline lens. Again, the greater the absorption by the crystalline lens, the greater the threat to the lens. Increased absorption is typical in older patients.[6] The most important optical parameters for the Panfunduscope are compared in the Table to those obtained with the Goldmann lens. The

TABLE
OPTICAL PROPERTIES OF THE GOLDMANN CONTACT LENS, THE PANFUNDOSCOPE, AND THE CGR 3 CONTACT LENS

PROPERTY	GOLDMANN	PANFUNDOSCOPE	CGR 3
Optical power (D)	−64	+50	−50
Magnification*	1	0.82	0.75
Field of view (deg)	±23	±83	±32
Spot diameter on the retina for a spot of 50 μm in air (μm)	55	65	70
Cone angle in vitreous for a cone angle of 6 deg in air (deg)	4.1	3.45	3.2
Laser beam diameter on the posterior face of the crystalline lens for a 1-mm spot on the retina (mm)	2.16	0.69/1.29	1.69

*The magnification with the Goldmann lens is taken arbitrarily equal to 1 because it is not possible to see the retina without a contact lens when using a slit lamp system. The other magnifications are then related to the magnification obtained with a Goldmann lens.

field of view is greatly increased, but the weakest point is the small spot diameter on the posterior face of the lens with 1-mm defocusing.

CGR 3 Contact Lens

The new CGR 3 contact lens* (Fig. 4) has been developed in an attempt to combine some of the particular features of the Goldmann lens (narrow-angle system) and the Panfunduscope (wide-angle system).

The CGR 3 is fitted with a concave anterior surface (Fig. 5). It creates an upright virtual image of the fundus, analogous to the simple Goldmann lens. The cone angles of both laser and observation beams are, however, reduced from 6 to 3.2 degrees. As a consequence, the field of view is increased from 46 to 64 degrees, which allows observation of a larger part of the posterior pole. The cone angle of the laser beam

*Manufactured by Lasag AG, Thun, Switzerland.

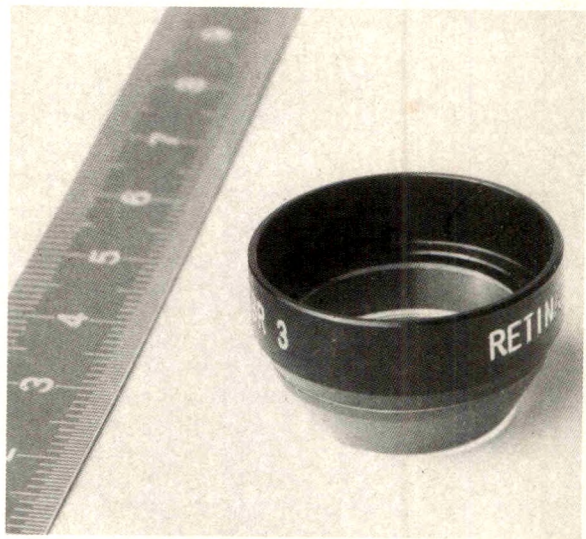


Fig. 4 (Rol, Fankhauser, and Kwasniewska). View of the contact lens CGR 3 for the observation and laser treatment of the retina.

is slightly smaller as compared to the Panfunduscope and the focal spot diameter is only slightly larger.

The most important optical parameters of the CGR 3 are compared in the Table to those obtained for the Goldmann lens. The field of view is greater than with the Goldmann lens and the spot diameter on the posterior face of the lens is not as small as with the Panfunduscope for a 1-mm defocusing. The increase of the minimum available spot size (which in most available laser systems is 50 μm) by a factor of 1.3 as compared with the Goldmann lens may at first appear to be a disadvantage. However, the size of the coagulation effect depends greatly on the duration of the exposure and pulse power and to a lesser extent on the geometric focus diameter.[7] By varying the power density,

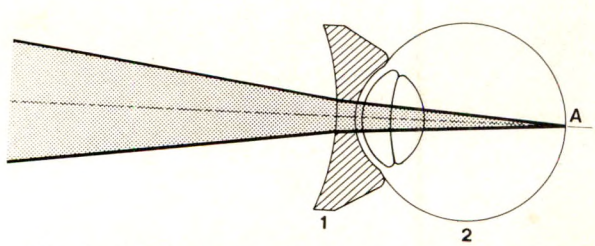


Fig. 5 (Rol, Fankhauser, and Kwasniewska). Diagram showing the optical path through the contact lens CGR 3. 1, CGR 3 lens; 2, human eye; A, focus point on the retina.

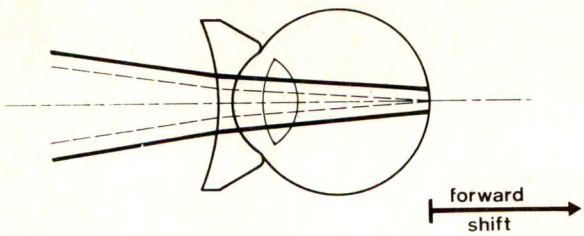


Fig. 6 (Rol, Fankhauser, and Kwasniewska). Shift of the laser beam to obtain a spot diameter on the retina of about 1 mm with the CGR 3. The dotted line represents the initial location of the beam to obtain the smallest spot size on the retina. The arrow indicates the direction of the shift.

small coagulation effects may be realized, even when the geometric focus spot is large.[8,9]

While the large field of view obtained with the Panfunduscope is lost, the CGR 3 enables safe forward defocusing, just as the Goldmann lens. This is true even when a laser spot as large as 1 mm is required (Fig. 6).

Discussion

For chorioretinal irradiation, the CGR 3 lens is a good compromise between the Goldmann lens and Panfunduscope. We have used it on about 100 eyes during observation or irradiation using the argon laser and the Nd:YAG laser working in the thermal mode (unpublished data).

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OPHTHALMIC MINIATURE

He has many categories of sight, ranged
In little boxes, a long, a short, an astigmatism
In a prism of glass. His machinery
Flickers an instant before me, lenses
You'd love to turn in your hand
Like ovals of limestone, waxy as opal.

Hilary Davies, "The Ophthalmologist"
Times Literary Supplement, September 4, 1987

Atypical Retinitis in Patients With the Acquired Immunodeficiency Syndrome

Mark T. Fay, M.D., William R. Freeman, M.D., Clayton A. Wiley, M.D., David Hardy, M.D., and Samuel Bozzette, M.D.

We examined three patients with AIDS who had large, sharply demarcated areas of thinned retina consistent with inactive cytomegalovirus retinitis and who were not treated with ganciclovir. These lesions appeared identical to clinically inactive areas of cytomegalovirus retinitis after effective antiviral treatment. All patients were receiving azidothymidine or ribavirin, or both, which have activity against the human immunodeficiency virus and which may improve immune function. All patients also received oral acyclovir at doses ineffective against cytomegalovirus retinitis.

CYTOMEGALOVIRUS RETINITIS is the most frequent ophthalmic opportunistic infection in patients with the acquired immunodeficiency syndrome (AIDS), occurring in 12% to 46% of this population.[1,2] In AIDS patients who do not receive specific anticytomegalovirus treatment, cytomegalovirus retinitis is a progressive and devastating infection ultimately leading to blindness.[2-7] Concomitant systemic infection with cytomegalovirus has been shown in these individuals.[7,8] An effective therapy for cytomegalovirus retinitis in AIDS patients is the experimental drug ganciclovir.[2,4,7] In non-AIDS patients, particularly immunosuppressed transplant recipients, restoration of immune function has been shown to cause regression and healing of cytomegalovirus retinitis.[9] We examined three AIDS patients with retinal lesions typical of cytomegalovirus retinitis who, without specific anticytomegalovirus therapy, demonstrated large areas of inactive retinitis consistent with partial or completely regressed cytomegalovirus infection. All three patients were receiving one or both antiretroviral drugs ribavirin or azidothymidine. Ribavirin may have activity against the human immunodeficiency virus (HIV), but it is not clinically effective against cytomegalovirus.[10] Studies have shown that azidothymidine, now called zidovudine, has no activity against cytomegalovirus (G. Edward Collins, R.Ph., Burroughs Wellcome Company, September 1987, oral communication). All patients had also received oral acyclovir for systemic herpes infection. Clinical trials show that acyclovir is not clinically active against cytomegalovirus retinitis when administered at standard doses.[11,12] Patients treated with anti-HIV therapy may have improved immune status, which may contribute to healing of cytomegalovirus retinitis, analogous to the healing of retinitis in transplant recipients after cessation of immunosuppressive agents. Alternatively, combinations of these drugs may have some direct anticytomegalovirus activity. A third possibility is that the retinitis in these patients represents herpes simplex or varicella zoster retinitis. Only the former is treatable with oral acyclovir. However, herpes simplex retinitis in AIDS patients is extremely rare and manifests clinically as a much more fulminant retinitis, called the acute retinal necrosis syndrome.[13]

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From the Departments of Ophthalmology (Drs. Fay and Freeman), Pathology (Dr. Wiley), and Medicine (Drs. Hardy and Bozzette), University of California at San Diego School of Medicine, La Jolla, California. This study was supported by a grant from the state of California.

Reprint requests to William R. Freeman, M.D., University of California, San Diego, M-018, La Jolla, CA 92093.

Case Reports

Case 1

A 39-year-old man with AIDS was examined on Aug. 8, 1986, with a four-month history of visual field loss. AIDS-related complex had been diagnosed in March 1984. In August 1984

he developed cryptococcemia, an AIDS-defining opportunistic infection, and was treated with amphotericin B and flucytosine. Shortly thereafter, he began self-treatment with ribavirin. In January 1986 he developed *Mycobacterium avium-intracellulare* bacteremia and was treated with sulfamethoxazole/trimethoprim followed by the combination of rifampin, ethambutol, ciprofloxacin, and amikacin. Shortly before examination, he developed disseminated varicella zoster. On examination, he was taking oral acyclovir, 4 g/day; ribavirin, 600 mg/day; ciprofloxacin, 1,500 mg/day; rifampin, 600 mg/day; and ethambutol, 800 mg/day.

Visual acuity was R.E.: 20/30 and L.E.: 20/20. Results of the anterior segment examination were normal in both eyes. The right eye showed a small amount of vitreous debris and retinal thickening at the superior border of a large area of inferior atrophic retina (Fig. 1). The left eye showed a small area of retinal thickening along the superotemporal arcade. Ciprofloxacin was discontinued and the patient was treated with ganciclovir because of possible active cytomegalovirus retinitis in the left eye. After three weeks of therapy his vision remained stable and atrophic retina with hyperpigmented retinal pigment epithelium was seen inferiorly in the right eye. In the left eye an area of retinitis had developed along the superotemporal arcade and showed signs of healing. On Nov. 25, 1986, the patient became neutropenic and the ganciclovir was stopped. On Dec. 8, 1986, visual acuity was R.E.: 20/20 and L.E.: 20/40. The retinitis had minimally progressed, his white blood cell count had stabilized, and ganciclovir was reinstituted. The patient died six weeks later of bacterial pneumonia.

Pathologic examination of the right eye of Patient 1 showed atrophic, thinned retina in the inferior fundus. Grossly, the area of atrophy occupied the entire inferotemporal quadrant and part of the inferonasal quadrant from the 4 o'clock to the 9 o'clock meridians, from the ora serrata to the optic nerve. Light microscopy demonstrated retinal gliosis in the atrophic area, a sharply demarcated junctional area, and retinal tissue with adjacent cytomegalovirus inclusions (Fig. 2). On histopathologic examination, cytomegalic cells with inclusions were seen in necrotic cells in areas of relatively well-preserved retinal structure (Fig. 3) as well as in necrotic areas (Fig. 4). Cytomegalic cells stained positive for human cytomegalovirus using polyclonal goat anti-human cytomegalovirus antibody (Fig. 5).[14] The infected cells were seen most prominently in the inner retina. Stains for HIV using monoclonal anti-human immunodeficiency virus antibody to GP41 protein were negative in areas of atrophic, gliotic, necrotic, and normal retina as were stains with anti-herpes simplex virus antibody.[15] Double-labeled immunocytochemistry for cytomegalovirus and factor VIII-related antigen, specific to endothelial cells (Fig. 6), and double-labeled immunocytochemistry for cytomegalovirus and neurofilament protein (Fig. 7) showed that both neuronal cells and an occasional endothelial cell were infected with cytomegalovirus.

Gross pathologic examination of the left eye showed an area of atrophic retina in the superotemporal and superonasal quadrants from the 11 to the 3 o'clock meridians, from the ora serrata to the optic nerve. Histopathologic examination showed cytomegalovirus inclusions in normal and necrotic retina. The inclusions stained positive for human cytomegalovirus; immunostaining for HIV was negative. Immunostaining of both eyes with rabbit polyclonal anti-herpes simplex virus and anti-varicella zoster virus was negative.

Case 2

A 33-year-old man with AIDS was examined on July 14, 1987, because of decreased vision and floaters in his left eye. In June 1986 he had had *Pneumocystis carinii* pneumonia. AIDS had been diagnosed at that time. He had *Salmonella arizonae* septicemia in October 1986, which recurred in December 1986. Disseminated *Mycobacterium avium-intracellulare* infection was diagnosed in January 1987 and he was treated with isoniazid, ethambutol, and rifampin. On our initial examination, he suffered from recurrent perianal herpes simplex infection and oral candidiasis. He had taken ribavirin from April 1987 to May 1987 and azidothymidine continuously since May 1987. The patient had also received oral acyclovir since April 1987. He was not taking any known anticytomegalovirus medication.

Visual acuity was R.E.: 20/30 and L.E.: 20/70. Results of the anterior segment examination were normal in both eyes. In the right eye there was a well-demarcated area of retinal atrophy, increased pigmentation, old vitreous condensations, and a sheathed vessel inferonasally. In the left eye there was a broader, well-demarcated, large atrophic area, with sheathed vessels and vitreous condensations in the nasal midperipheral retina (Fig. 8). The diagnosis of healed cytomegalovirus retinitis was suggested by the clinical findings. Blood cultures for cytomegalovirus on two separate occasions were

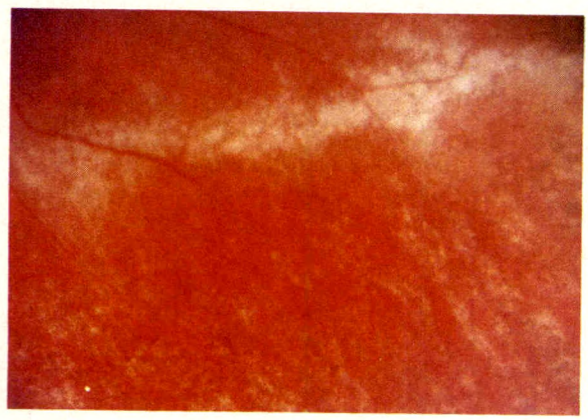


Fig. 1 (Fay and associates). Case 1, right eye. Inferonasal area showing a broad area of thin atrophic retina with a narrow zone of retinal whitening consistent with recent reactivation of retinitis or incomplete healing.

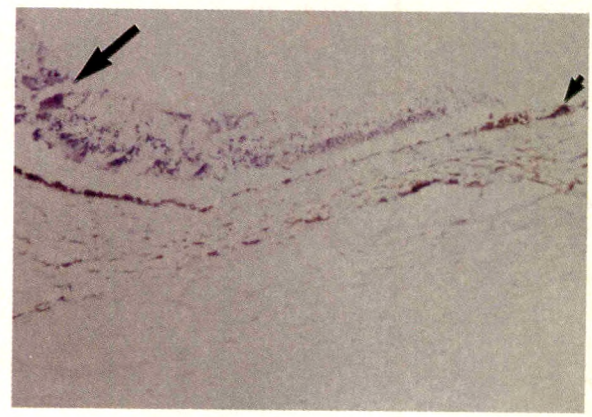


Fig. 2 (Fay and associates). Case 1, right eye. Junctional area of healed retinitis. The junctional zone (large arrow) shows retinal necrosis and is adjacent to the gliotic retina (small arrow) (hematoxylin and eosin, ×80).

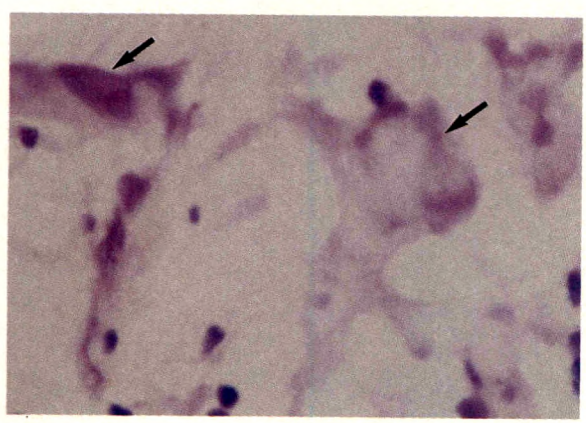


Fig. 3 (Fay and associates). Case 1. High-power view of partially necrotic retina. Note enlarged cytomegalic cells with inclusions (arrows) (hematoxylin and eosin, ×80).

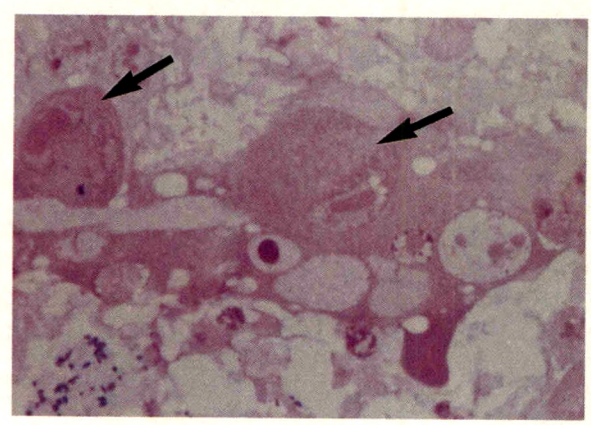


Fig. 4 (Fay and associates). Case 1, 0.5-μm section. Necrotic area shows enlarged cell with typical cytomegalovirus inclusions (arrows). The pigment epithelium contains typical pigment granules (hematoxylin and eosin, ×800).

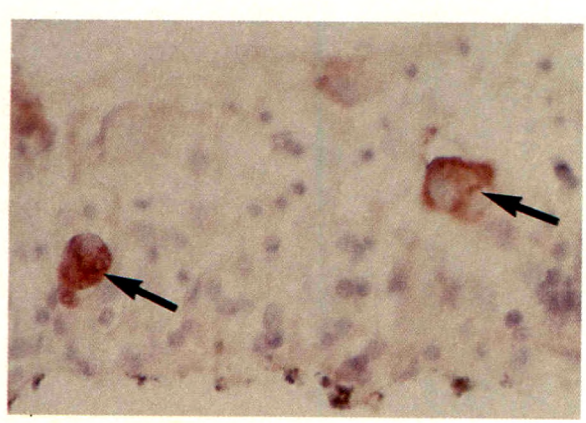


Fig. 5 (Fay and associates). Case 1. Staining (red) with polyclonal anti-human cytomegalovirus antibody (arrows) (immunoperoxidase, ×200).

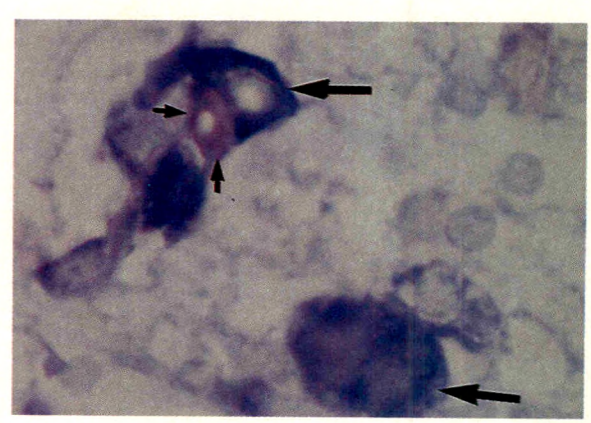


Fig. 6 (Fay and associates). Case 1. Necrotic cells stain with anticytomegalovirus antibody (blue, large arrows) and anti-endothelial cell second immunostain (red) labels endothelial cells (small arrows). Occasional cells (central cell) are cytomegalovirus-infected endothelial cells (double-labeled, ×800).

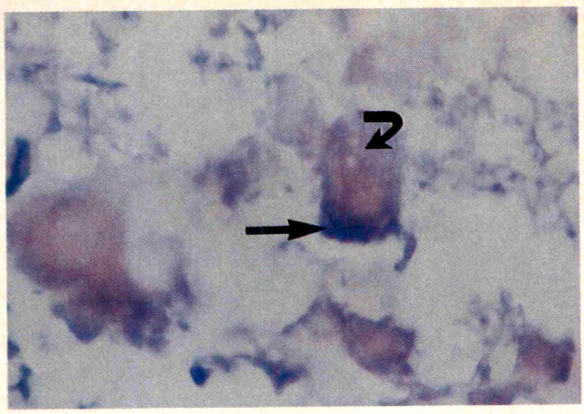


Fig. 7 (Fay and associates). Case 1. Same area as in Figure 6 shows staining with anticytomegalovirus antibody (blue, large arrow) neurofilament protein (red), which marks nonglial, neuronal cells. Most of the cytomegalovirus-infected cells are neuronal and stain with both reaction products (curved arrow) (double-labeled, ×800).

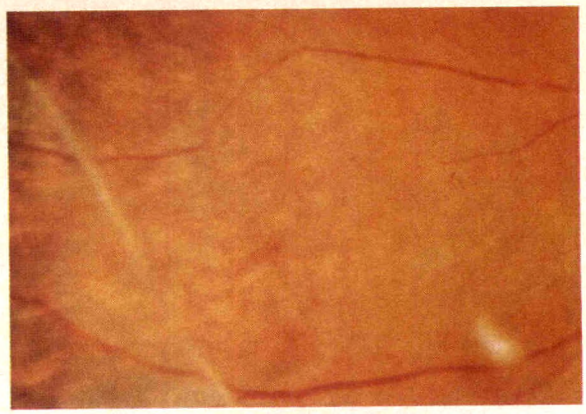


Fig. 8 (Fay and associates). Case 2, left eye. Nasal fundus photograph showing untreated healed retinitis. Atrophic retina is seen with overlying vitreous condensations.

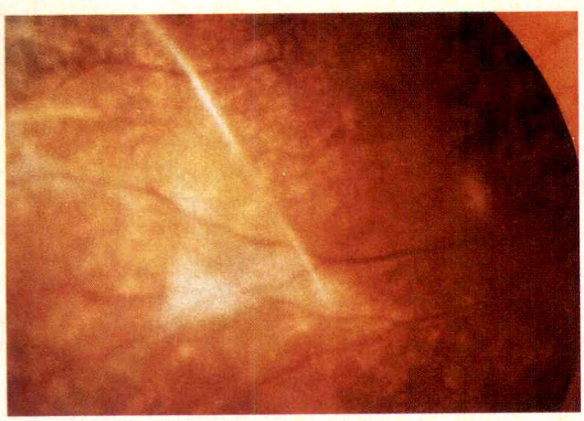


Fig. 9 (Fay and associates). Case 2, left eye. Inferonasal fundus photograph six weeks later. No anticytomegalovirus therapy was administered and the appearance is unchanged. The vitreous condensation is in a different position.

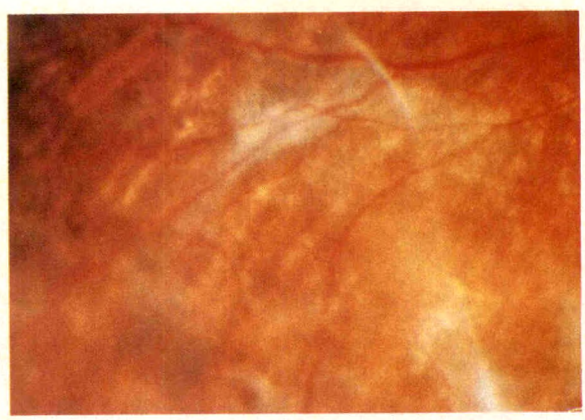


Fig. 10 (Fay and associates). Case 2, left eye. Inferonasal fundus photograph ten weeks later. No specific anticytomegalovirus therapy was administered. The appearance of the healed retinitis is unchanged. The patient received azidothymidine therapy during the period of observation.

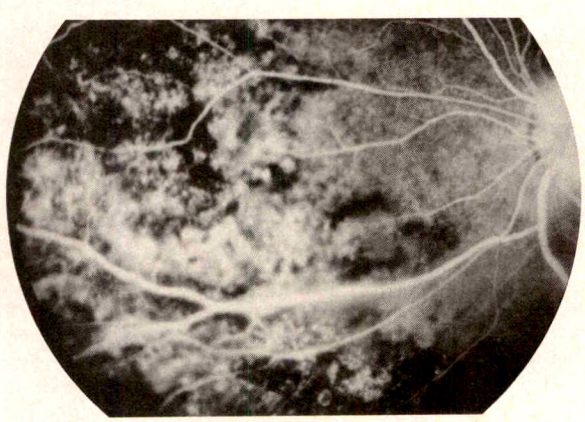


Fig. 11 (Fay and associates). Case 2. Fluorescein angiogram, mid phase at initial examination shows mottled hypofluoresence with early mild vascular leakage.

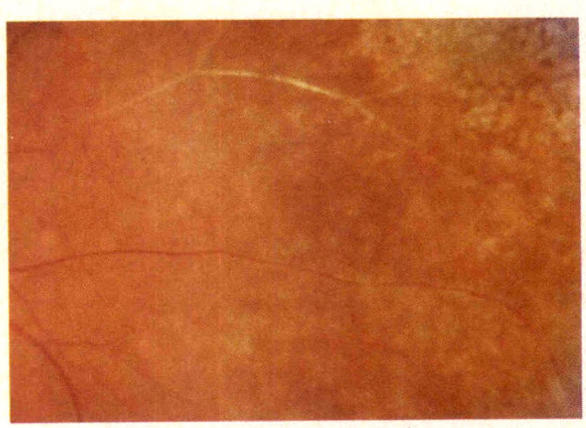


Fig. 12 (Fay and associates). Case 3, right eye. Nasal area showing healed retinitis.

negative. Two, six, and 11 weeks after the initial examination the patient was observed and rephotographed (Figs. 9 and 10). The appearance of the retina was unchanged in both eyes. The fluorescein angiogram performed on July 14 disclosed broad areas of nonperfused, atrophic retina corresponding to the areas described above, inferonasally in the right eye and in the nasal midperiphery of the left eye. Late staining of the vitreous was seen, presumably secondary to breakdown of the blood-retinal barrier. No fluorescein leakage from the borders of the lesions was seen (Fig. 11).

Case 3

A 34-year-old man with AIDS had a two-month history of decreased vision associated with floaters and flashing lights. His medical history was significant for *Pneumocystis carinii* pneumonia and disseminated *Mycobacterium avium-intracellulare*. Medications included 500 mg of sulfadiazine and 25 mg of pyrimethamine per week, 300 mg of isoniazid per day, 200 mg of acyclovir twice daily, 300 mg of theophylline three times daily, 200 mg of ketoconazole twice daily, and 300 mg of rifampin twice daily. He had also been treated with azidothymidine for one month before ocular examination. On examination, visual acuity was R.E.: 20/20 and L.E.: 20/50. The anterior segment examination showed corneal keratic precipitates in both eyes; there was no cell or flare in the anterior chambers. In the right eye there were broad areas of atrophic retina superotemporally, beginning just outside the macula. The entire nasal retina was atrophic, with underlying hyperpigmentation of the pigment epithelium. There was a broad atrophic area of retina seen inferiorly in the left eye. The only area of active retinitis was along the superonasal arcade in the left eye. In all other areas the retina had an atrophic, healed appearance; the patient refused to be photographed. He had not been taking any anticytomegalovirus medication. The patient was treated elsewhere with ganciclovir and was not reexamined until eight weeks later. The appearance of the right eye was unchanged (Fig. 12). In the left eye there was decreased whitening of the superonasal area of retinal thickening.

Subjects and Methods

The records of the last ten consecutive AIDS patients with cytomegalovirus retinitis followed up by one of us (W.R.F.) with high-quality, serial fundus photographs during ganciclovir treatment were reviewed to determine the characteristics and course of healing. All patients were examined by one of us (W.R.F.). Fundus photographs were taken using a wide-angle camera where possible, and an attempt to photograph all areas of involvement was made. The photographs and clinical charts were then reviewed by another of us (M.T.F.). Selected cases were reviewed from the literature for comparison,[1,5,7] and the characteristics and course of healing were noted. These data were used for comparison with the patients in this study who were not treated with ganciclovir.

Sections from the eye of Patient 1 were studied by immunocytochemistry as previously described.[14,15] Rabbit antiserum against herpes simplex viral antigen was diluted 1:50 according to commercial protocols (DAKO, Santa Barbara, Calif.). Mouse monoclonal antibody to GP41 of HIV was used at a dilution of 1:50. Goat polyclonal antiserum to cytomegalovirus (Polysciences, Warrington, Pa.) was used at a dilution of 1:50. After endogenous peroxidase and nonspecific immunoglobulin binding were blocked, sections were incubated in the primary antiserum for two hours at room temperature. Sections were extensively washed and then incubated for one hour at room temperature with appropriate biotinylated secondary antibodies diluted 1:50 (TAGO, Burlingame, Calif.). Sections were again extensively washed before incubation in either an avidin-biotin-horseradish peroxidase complex (DAKO) or an avidin alkaline phosphatase complex (Miles Laboratories, Naperville, Ill.). Reactions were developed with either aminoethylcarbazole or fast-blue substrates. For double-labeled immunocytochemistry, sections were first stained for cellular antigens with the phosphatase reaction using a fast-blue substrate. A second series of antibody staining was then performed followed by a nonbiotinylated goat anti-mouse immunoglobulin, mouse antiperoxidase/peroxidase complex, and with aminoethylcarbazole substrate.

Results

Review of our patients who had high-quality serial fundus photographs and retinal drawings while undergoing ganciclovir treatment for cytomegalovirus retinitis showed that the

early signs of regression of retinitis were nonadvancement of edges, decreased satellite lesions, or confluence of retinitis to the initial satellite lesions. This was followed by thinning, increased granularity and yellowing or graying of the white fluffy exudative areas, improved demarcation of the lesions, decreased hemorrhage, and vessel wall sclerosis. Late signs of healing were increased pigmentation and thinning of atrophic retina, gliosis, and increased refractile deposits. Ghost vessels with sclerotic-appearing vessel walls remained after healing. Signs of healing began at two weeks and were usually complete by six to ten weeks.

Discussion

The diagnosis of cytomegalovirus retinitis is usually made by its characteristic clinical appearance.[1,6,7,16] The typical pattern of retinal hemorrhage and granular whitening is often seen in the posterior pole representing intraretinal hemorrhage, edema, and necrosis. Dense areas of retinal necrosis often occur initially along the vascular arcades, and may be associated with retinal vasculitis, exudates, and vitritis.[17] This posterior pole cytomegalovirus retinitis is characteristically well demarcated. Peripheral retinitis usually shows less intense, less well-demarcated whitening, with areas of granular retinitis, and occasionally with scattered hemorrhages.[7] There may be involvement of the optic nerve as well as anterior uveitis.[17] The many reports of culture- and biopsy-proven cytomegalovirus retinitis indicate that the appearance is characteristic.[3,18-22] These patients usually have positive urine culture for cytomegalovirus and almost always have cytomegalovirus infection elsewhere.[4,7,8] Viruses other than cytomegalovirus can also cause retinitis; however, the appearance is different. Retinal infection with herpes simplex virus and varicella zoster is a more fulminant disease, often associated with the syndrome of acute retinal necrosis, and characterized by rapid progression of retinitis, prominent inflammatory signs, broad areas of retinal necrosis, and retinal detachment.[13,23]

A treatment shown to be effective for cytomegalovirus retinitis is ganciclovir, formerly called dihydroxy propoxymethyl guanine.[1,2,7,24,25] It halts the progression of retinitis and causes decreased edema and inflammation, leaving atrophic pigmented areas of retina similar to the clinical picture seen in our three patients. Other agents have been found to be unsuccessful in treating cytomegalovirus retinitis, including acyclovir, alpha-interferon, vidarabine, prednisone, and laser photocoagulation.[24,26,27] Phosphonoformate has not been widely used but may have some efficacy.

The characteristics of healing of cytomegalovirus retinitis have been identified both in iatrogenically immunosuppressed patients when the immunosuppressive therapy has been discontinued, and in patients treated with the anticytomegalovirus drug ganciclovir. In iatrogenically immunosuppressed patients, regression of the retinitis occurred in an average of ten weeks (range, four weeks to four months) after cessation of the immunosuppressive therapy.[28] Markers of regression in these patients were loss of satellite lesions, absence of venous sheathing outside the area of retinal necrosis, a harder appearance to the edge of the lesion, and absence of advancement of the edges. The color of the lesion changed to gray or yellow, and the lesion became thinner, leaving a thin translucent retinal scar. Histologically, all layers of the retina were destroyed, leaving an intact internal limiting membrane.[28]

The response of cytomegalovirus retinitis to ganciclovir in AIDS patients has been described to have a similar course. Early response is characterized by a decrease in retinal opacification occurring over a two- to three-week period. A failure of lesion borders to advance has been emphasized by most investigators.[2,25] Resolution of hemorrhage and vasculitis also occurs.[2]

The possibilities for inactivity of the cytomegalovirus retinitis in our three patients who were not treated with ganciclovir or specific anticytomegalovirus therapy include improved immunocompetence or anticytomegalovirus activity of drugs other than ganciclovir. Before ophthalmologic examination, Patients 1 and 2 had been taking ribavirin, an experimental anti-HIV drug. Ribavirin has been shown to be effective against RNA viruses such as respiratory syncytial virus, and is reported to have antiretroviral activity against HIV in vitro, although the clinical efficacy is questionable.[29] Ribavirin has not been shown to be clinically effective against DNA viruses such as cytomegalovirus (Table).[10]

Patients 2 and 3 were treated with azidothymidine, now called zidovudine. Azidothymidine is a thymidine analogue that inhibits HIV replication in vitro.[30] The human immunodeficiency virus is a retrovirus, meaning viral RNA must code for the formation of a DNA

TABLE
ACTIVITY OF ANTIVIRAL DRUG THERAPY

ACTIVITY	AZIDOTHYMIDINE	RIBAVIRIN	ACYCLOVIR
Anticytomegalovirus activity	No	No	No*
Anti-HIV activity	Yes	Yes	No
Improved immune function	Yes	Possible	No

*No effect in clinical trials. In vitro levels higher than clinically attainable have some activity against certain strains of cytomegalovirus.

reverse transcriptase before the virus can replicate. Azidothymidine competitively inhibits HIV reverse transcriptase and is incorporated into viral DNA, resulting in chain termination. Azidothymidine has been shown to restore partial immune function in AIDS patients. Patients treated with azidothymidine can show a twofold to threefold increase in the number of T helper-inducer (CD4) lymphocytes at eight to 12 weeks of treatment, and a return of cutaneous hypersensitivity reactions has been reported in some previously anergic individuals. An increase in survival has also been demonstrated.[30] Azidothymidine has no in vitro or clinical activity against cytomegalovirus.

All three patients had also been treated with acyclovir (Table). Although acyclovir is active against some strains of cytomegalovirus at high concentrations, these levels were not achieved at the doses administered to our patients.[11,12] We cannot rule out the possibility of synergistic activity of two or more antiviral drugs against cytomegalovirus.

These three patients demonstrate regressed retinitis without specific anticytomegalovirus treatment. This appearance is characterized by broad areas of thinned retina associated with pigmentation and evidence of previous cytomegalovirus retinitis. These patients may have experienced improved immune status associated with antiretroviral activity of azidothymidine or ribavirin, analogous to healing of cytomegalovirus retinitis in iatrogenically immunosuppressed patients after discontinuation of immunosuppressive drugs. We cannot definitively rule out direct anticytomegalovirus activity of azidothymidine, ribavirin, or acyclovir, but there is no experimental or clinical evidence that such activity exists at the doses used by our patients.

As more AIDS patients are treated with effective anti-HIV drugs that improve immune function, the clinical appearance of regressed retinitis or a retinitis with atypical features may become common. Ophthalmologists should be aware that in AIDS patients treated with new immunostimulating and anti-HIV drugs, cytomegalovirus retinitis may take on an atypical appearance and course; knowledge of this will enable more rational therapeutic decisions. Indeed, concurrent treatment with azidothymidine or other antiretroviral drugs may allow lower and less toxic doses, or modified delivery schedules, of anticytomegalovirus drugs such as ganciclovir. As better modalities of improving the immune function of AIDS patients are developed, the indications for specific anticytomegalovirus therapy in these patients may be significantly changed.

ACKNOWLEDGMENT

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Ultrastructural Characteristics of New Vessels in Proliferative Diabetic Retinopathy

John M. Williams, Sr., M.D., Eugene de Juan, Jr., M.D., and Robert Machemer, M.D.

We studied the ultrastructural characteristics of 23 vascularized preretinal membranes removed from 22 eyes during pars plana vitrectomy for proliferative diabetic retinopathy. Traction detachment of the macula was the most frequent reason for surgery (15 of 22 eyes), followed by nonclearing vitreous hemorrhage (seven of 22 eyes). Vessels found in the membranes were studied by serial sectioning and categorized as having either developing, mature, or regressing characteristics. Developing vessels were seen in ten of 23 membranes (43%), mature vessels in 19 of 23 membranes (83%), and regressing vessels in 13 of 23 membranes (57%). Endothelial fenestrations and cell separations were rare. With three-dimensional reconstruction, we found that new vessels often extended cytoplasmic processes into the extracellular matrix and that lumina were present even at the distalmost tips of the vessels. Solid cords of endothelial cells were not seen.

We concluded that in proliferative diabetic retinopathy, new vessels develop by a process of focal extracellar matrix degradation, generalized and exuberant extracellar matrix production, cytoplasmic microvillus extension into the extracellular matrix, and active lumen formation.

In the United States, diabetic retinopathy is the leading cause of new cases of blindness in patients less than 60 years of age.[1] The development of pars plana vitrectomy[2] has allowed treatment of the most severe manifestations of proliferative disease such as traction retinal detachment and nonclearing vitreous hemorrhage. Vitrectomy is also useful for obtaining fresh tissue specimens of vascularized membranes. The ultrastructure of new vessels in proliferative diabetic retinopathy has been reported by relatively few authors[3-6]; moreover, the process of new vessel formation has not been described in patients with proliferative diabetic retinopathy. We studied the ultrastructure of new vessels in proliferative diabetic retinopathy by using three-dimensional reconstructions of serial sections of membrane obtained during vitreous surgery for proliferative diabetic retinopathy.

Material and Methods

Twenty-three vascularized preretinal membranes were removed from 22 patients with proliferative diabetic retinopathy. Clinical data regarding the reason for vitrectomy (age of patient, type of diabetes [I or II], duration of disease) were tabulated as well as whether preoperative laser photocoagulation was performed.

In the first 16 cases, specimens for transmission electron microscopy were prepared in the manner previously described by Hamilton and associates.[5] In the last seven membranes, 3% glutaraldehyde in 0.1 M cacodylate buffer was used for primary fixation instead of 2% glutaraldehyde in 0.1 M cacodylate buffer. Specimens for light microscopy were embedded in Epon and stained with methylene blue and azure II.

Serial sections (done on five highly vascular specimens) were taken in the following manner: ten to 20 1-μm thick serial sections were taken followed by a 1-μm section that was further divided into multiple 60- to 90-nm thin sections, which were again followed by a series of ten 1-μm thick sections. (Thus, the total

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length of contiguous sections ranged from 10 to 30 μm in length.) Thick sections were examined with light microscopy and thin sections with transmission electron microscopy. Serial photomicrographs were taken, and vessels were categorized as developing, mature, or regressing.

Based on experimental models of neovascularization in the rabbit cornea[7] and retina,[8] as well as in human cases of proliferative diabetic retinopathy,[3-6] we divided new vessels in diabetic retinopathy into three categories: developing, mature, and regressing. We categorized developing new vessels as those having thick walls and narrow lumina and demonstrating endothelial microvilli, both luminal and abluminal. These vessels were typically surrounded by an abundant multilayered basal lamina, which was fragmented at the sites of budding. Mature new vessels were classified as those having thin walls, wide lumina, and a well-formed basal lamina. Regressing new vessels were characterized as those demonstrating a loss of endothelial cell cytoplasmic and nuclear architecture. Stasis, thrombosis with formed blood elements, or both, may also be present. Cell wall discontinuities could be seen in these vessels, but the basal lamina typically remained as an intact single layer.

Results

The surgeries were performed between July 1977 and January 1985. The reason for vitrectomy was traction macular detachment in 15 patients and nonclearing vitreous hemorrhage in seven patients. The patients were generally young (average age, 39.1 ± 18.5 years), and Type I diabetes mellitus predominated (15 patients with Type I vs seven patients with Type II). The average duration of diabetes was 20.5 ± 7.9 years.

When all of the membranes were categorized as to the types of vessels they contained, it was found that developing vessels were seen in ten of the 23 membranes (43%) (Fig. 1). Endothelial intercellular gaps were not observed, and fenestrations were seen in developing vessels in only two of the ten membranes with this vessel type. These two membranes each had one fenestrated, developing vessel that could be identified. The fenestrations in these vessels were single. Mature new vessels were seen in 19 of the 23 membranes (83%), and fenestrations in these vessels were uncommon (five of 19 membranes, 26%). The membranes with fenestrated, mature vessels tended to have many vessels with these characteristics, and when fenestrations were found, they were usually multiple (Fig. 2). Regressing new vessels were seen in 13 of the 23 membranes (57%) (Fig. 3). Fenestrations were seen in regressing vessels in two of 13 membranes (15%) with this vessel type.

Examination of the serial sections allowed us to follow several budding vessels in three dimensions. Fragmentation of the basal lamina was present at the tips of many of the cytoplasmic extensions (Fig. 4). When a developing vessel was followed to its distal termination, it ended in a terminal bud and maintained a blood-filled lumen throughout its course (Figs. 5 and 6). This was better demonstrated when the vessel was computer-reconstructed in three dimensions (Fig. 7).

Most of the membranes had more than one type of vessel, and sometimes a single vessel would manifest characteristics of more than one vessel type. For example, one of the buds studied with serial sections demonstrated the developing characteristics of a bud originating from a mature venule (Fig. 8).

The membranes from patients with Type I diabetes mellitus usually had vessels from each of the three groups: developing, mature, and regressing. New vessels characterized as developing were seen almost exclusively in membranes from Type I diabetics. Additionally, most fenestrated vessels were seen in membranes from patients with Type I diabetes. Most of the vessels in membranes from patients with Type II diabetes were either mature or regressing, and fenestrations were rare at any stage. Finally, the presence of preoperative laser photocoagulation did not correlate with the type of vessels found in the membranes in either type I or type II diabetics.

Discussion

The process of retinal neovascularization in mammals has been a subject of controversy. Michaelson[9] described retinal vessel development in the cat as a process of capillary budding from preexisting vessels, probably venules. Ashton[10,11] believed the process involved a preliminary invasion by primitive mesenchymal cells that differentiated into endothelial

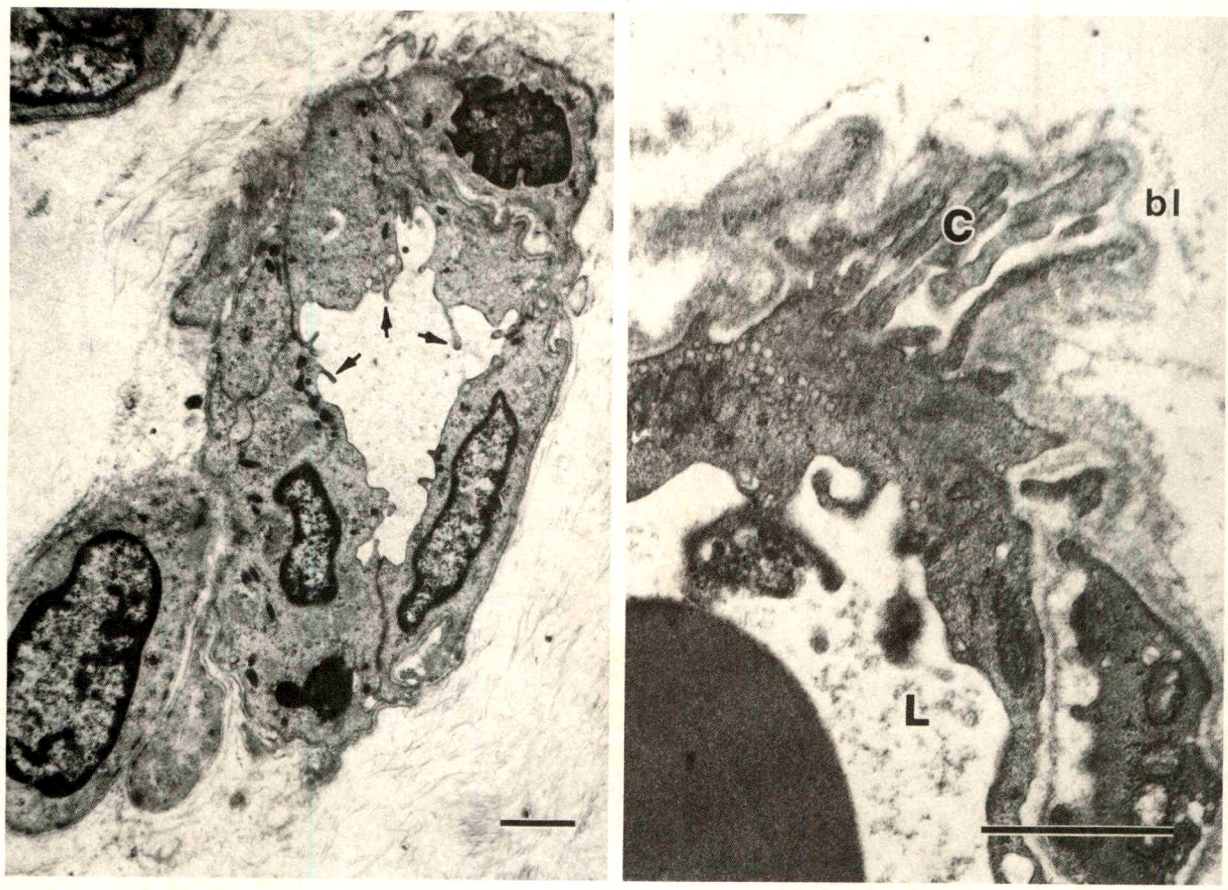


Fig. 1 (Williams, de Juan, and Machemer). Left, Developing new vessel. Note thick wall, narrow lumen, and luminal microvilli (arrows) (bar gauge = 1 μm; ×11,000). Right, Cytoplasmic extensions (C) from a developing new vessel project toward the surrounding multilayered basal lamina (bl) (L, lumen) (bar gauge = 1 μm; ×26,500).

cells, eventually forming a capillary network from which adult retinal vessels evolved. Henkind and de Oliveira[12] (in the india ink injected rat retina) showed that solid cords were present which were continuous with, but extended beyond, ink-filled vascular channels. Engerman and Meyer,[13] in a complete account of angiogenesis in the rat retina, found that primitive capillaries extended between and anterior to the tips of larger radial vessels. Thus, most studies of developing retina using light microscopy have suggested that solid cords of cells precede the development of vascular channels with accompanying lumina in normal retinal vascular development.

At the ultrastructural level, Ausprunk and Folkman[7] reported the histologic sequence of events occurring in tumor-induced capillary proliferation in the rabbit cornea. They found that endothelial cells extended pseudopods and migrated out of the walls of parent vessels (usually venules). Intercellular junctions were loose, and gaps were often present between endothelial cells that leaked colloidal carbon. The basal lamina was fragmented at the distal end of the capillary sprout and remained intact proximally.[14] De Juan and coworkers,[15] studying retinal neovascularization in the fibroblast-injected rabbit, found new vessels had thickened walls and narrow lumina and that they lacked gaps and fenestrations. Horseradish peroxidase did not leak from even the most immature new vessels although fluorescein leakage was prominent. The vessels developed by a process of luminal budding into an exuberant extracellular matrix that had multiple layers of basal lamina-like material surrounding the vessels. The basal lamina was fragmented only at the sites of budding.

Taniguchi,[3] as well as Wallow and Geldner,[4]

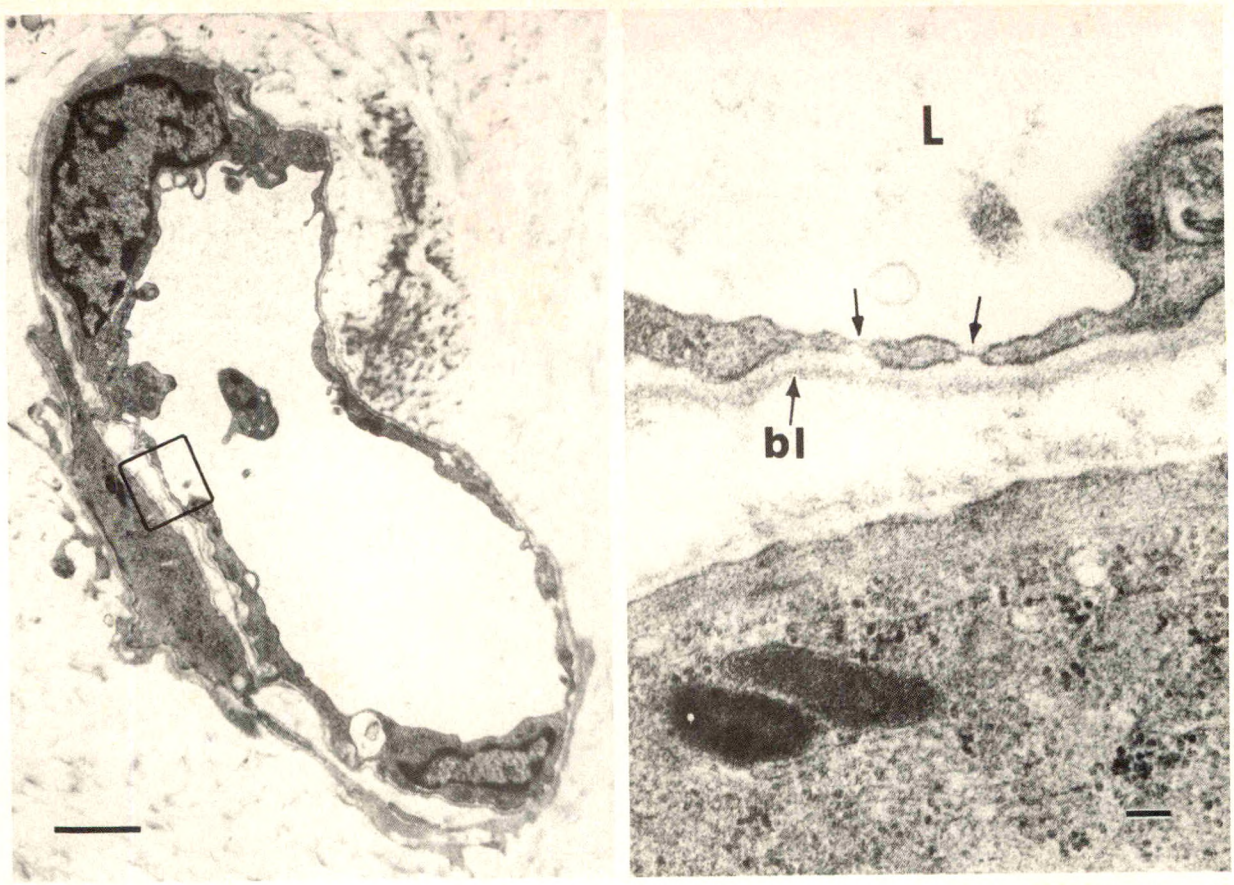


Fig. 2 (Williams, de Juan, and Machemer). Left, A vessel with some mature characteristics. Note the thin wall and wide lumen (bar gauge = 1 μm; ×12,000). Right, Enlargement of the vessel wall (inset, left) shows fenestrae (arrows) and a well-formed basal lamina (bl) (L, lumen) (bar gauge = 0.1 μm; ×60,000).

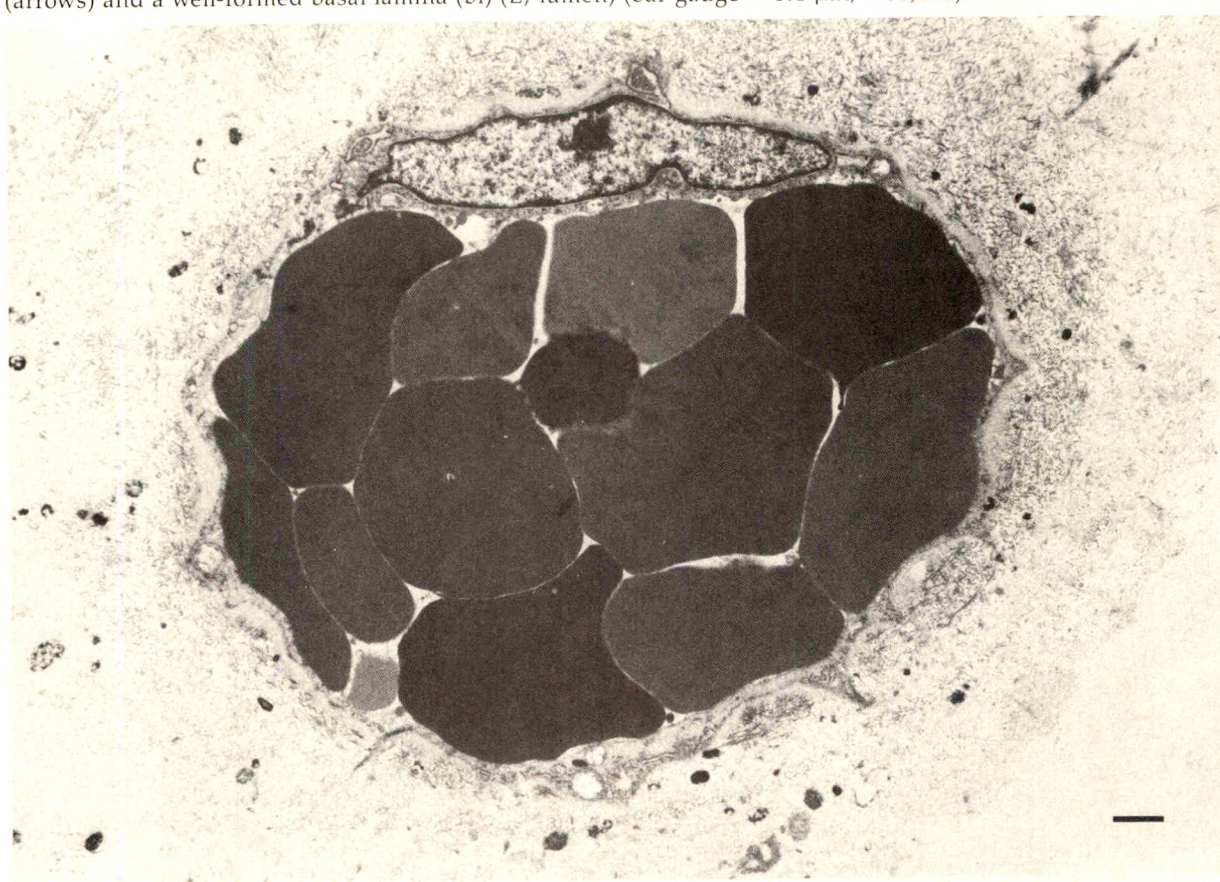


Fig. 3 (Williams, de Juan, and Machemer). Regressing new vessel. The lumen is occluded with red blood cells (bar gauge = 1 μm; ×7,000).

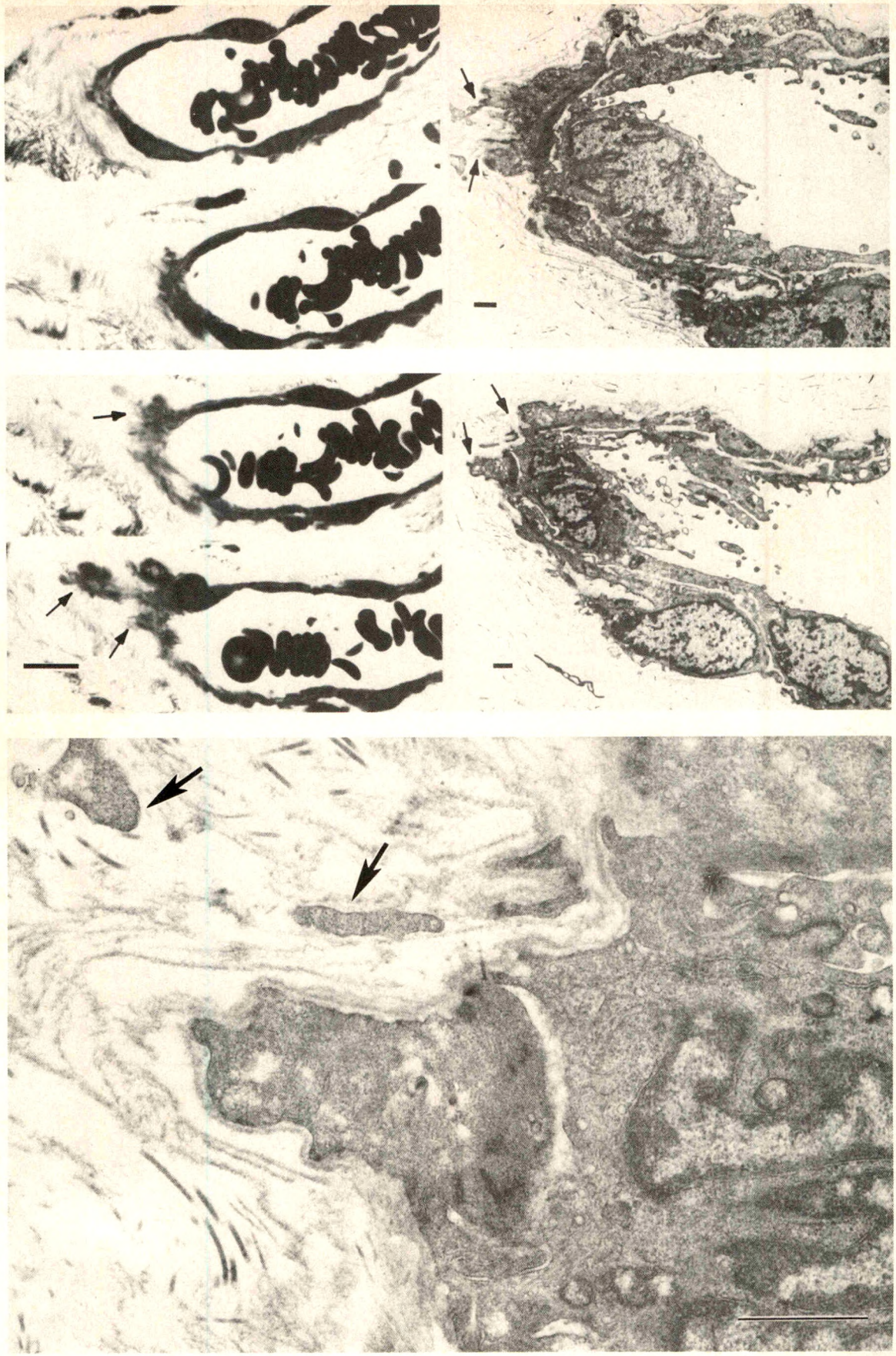


Fig. 4 (Williams, de Juan, and Machemer). Top left and bottom left, Serial sections through a budding vessel exhibiting cytoplasmic extensions (arrows) (bar gauge = 10 μm; ×950). Top right and bottom right, The same vessel when studied with transmission electron microscopy demonstrates fragmentation of basal lamina at the budding end of the vessel (arrows) (bar gauge = 1 μm; ×4,000, top; ×3,000 bottom). Bottom, Magnified view of endothelial cell cytoplasmic bud (arrows) (bar gauge = 1 μm; ×23,000).

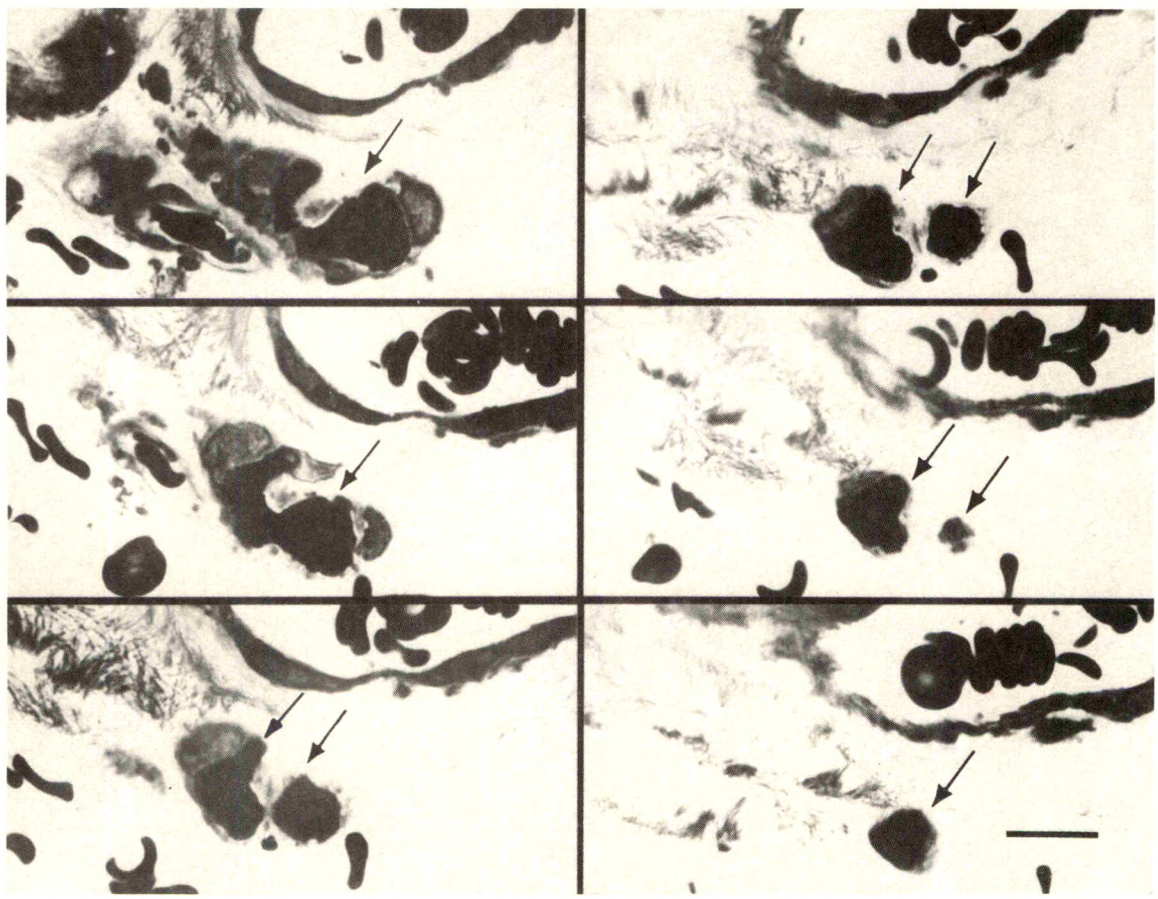


Fig. 5 (Williams, de Juan, and Machemer). Serial sections through a developing new vessel (arrow) that divides from one lumen to two (arrows), one of which ends in a blind bud (bar gauge = 10 μm; ×1,200).

examined the ultrastructural characteristics of preretinal membranes from human eyes (obtained at enucleation and autopsy, respectively) of patients with proliferative diabetic retinopathy. Both studies documented fenestrations in the vessels of these membranes and suggested their presence was a reason for the leaky nature and fragility of these vessels. Hamilton and coworkers[5] evaluated 30 preretinal membranes of patients who underwent vitrectomy for proliferative diabetic retinopathy. They found fenestrated capillaries in only four of 21 vascularized membranes (19%). Similarly, Miller and coworkers[6] noted rare fenestrations in the nine membranes they studied. Fenestrations were seen in only seven of 23 membranes (30%) in our study, and for the most part these were infrequently observed. Thus, we believe the bulk of evidence suggests that fenestrations are not sufficiently common in the new vessels to explain leakage of fluorescein. By this we mean that, although it is well known that preretinal neovascularization vessels typically leak fluorescein, not all (and probably few) contain fenestrations so other mechanisms of leakage must also be considered. The leakage could occur through incompetent or immature cell junctions,[4,6] directly across the endothelial cell wall by transport systems, or could be caused by abnormal basal lamina constitution. For example, in the kidney alterations in basal lamina may account for increased permeability observed in patients with diabetes mellitus.[16,17]

By applying the ultrastructural characteristics of experimentally induced developing new vessels from the retina in the rabbit[8,15] to membranes in proliferative diabetic retinopathy, three types of vessels could be characterized. We believe these correspond to developing (thick-walled, narrow-lumen vessels with cyto-

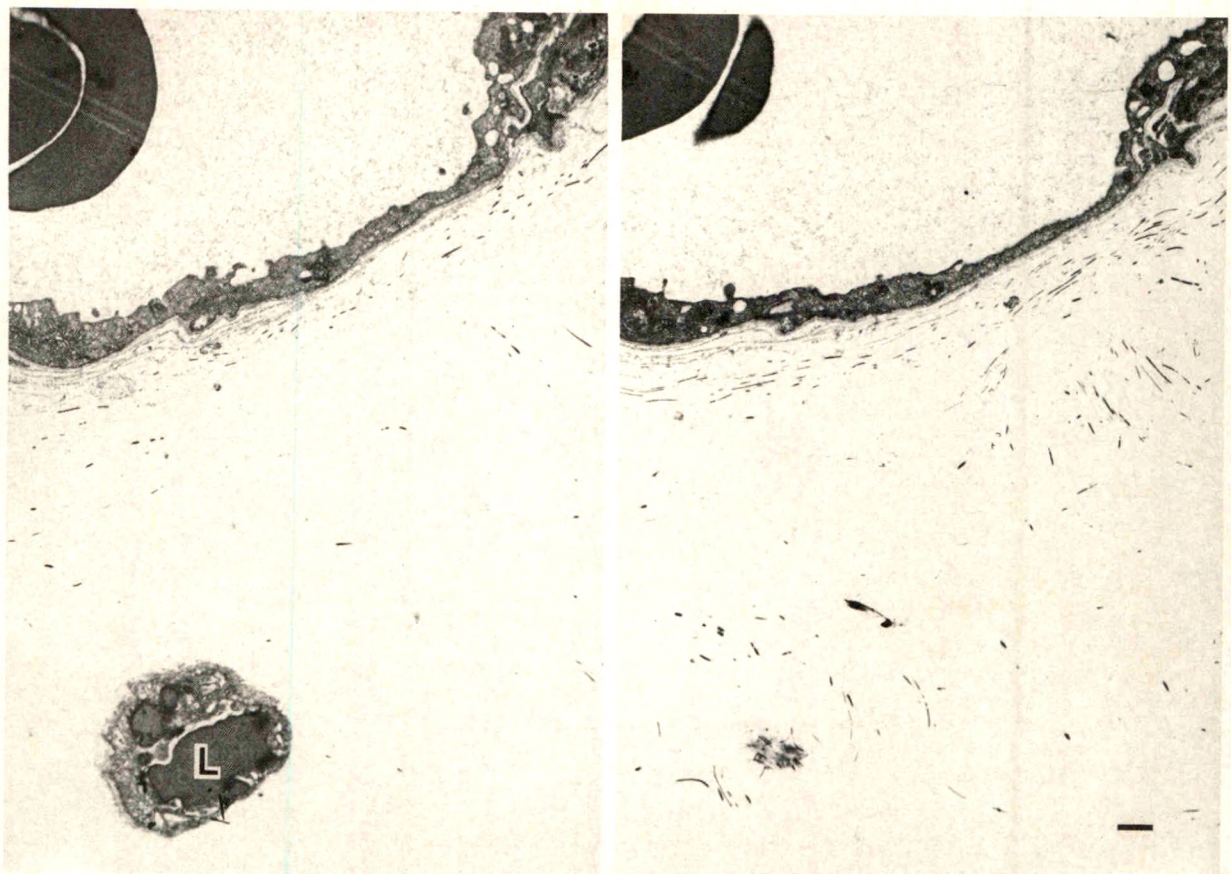


Fig. 6 (Williams, de Juan, and Machemer) Continuation of Fig. 5 when followed with thin sections. Left, The vessel has a lumen (L) with a red blood cell in it. Right, The vessel is not seen in the next section taken approximately 200 nm from the previous section (bar gauge =1 μm; ×5,000).

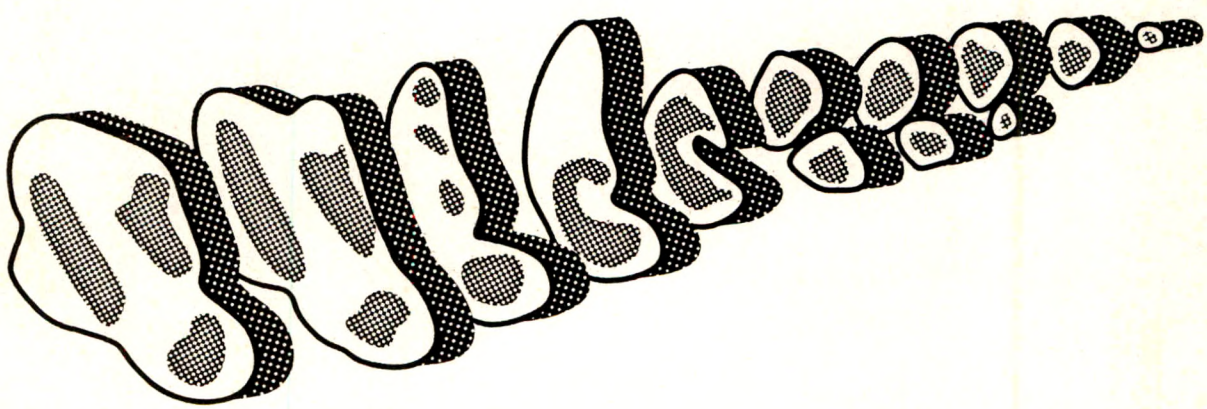


Fig. 7 (Williams, de Juan, and Machemer). Computer-generated reconstruction of the developing vessels seen in Figures 5 and 6. Cross-hatched areas correspond to lumina.

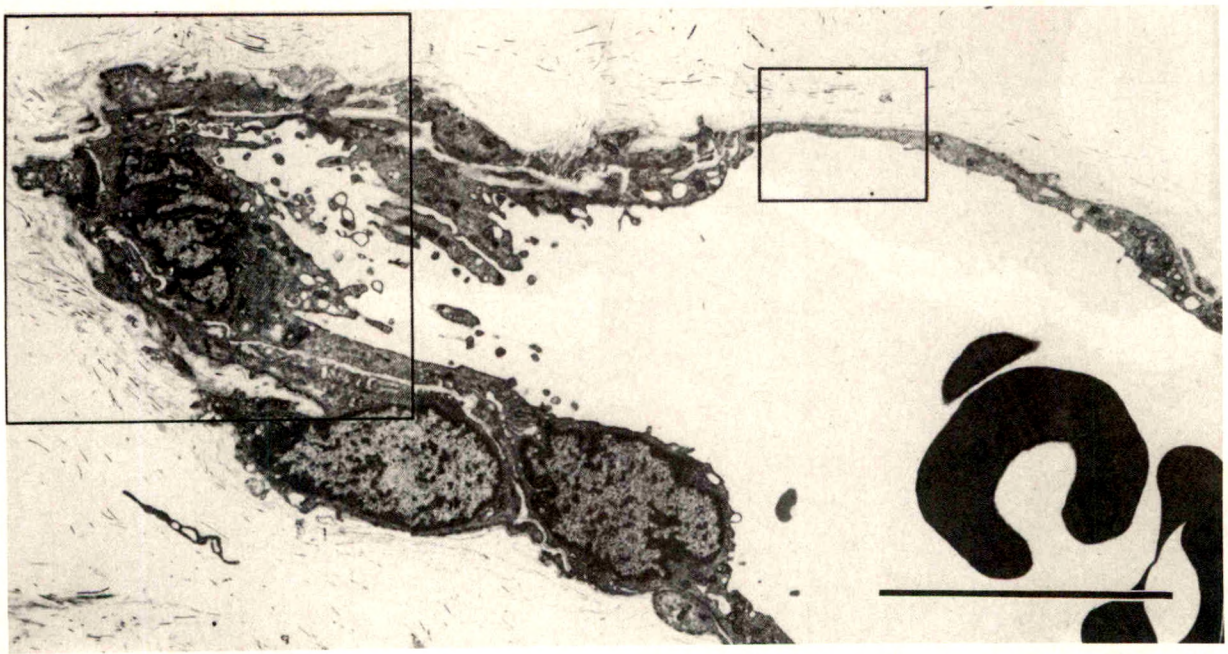


Fig. 8 (Williams, de Juan, and Machemer). Right inset, A venule with mature characteristics (thin wall, well-formed basal lamina, and wide lumen). Left inset, The vessel also demonstrates developing characteristics (narrow lumen, thick wall, fragmented basal lamina) (bar gauge = 10 μm; ×4,000).

plasmic extension into the extracellular space through fragmented basal lamina), mature (thin-walled, wider-lumen vessels with differentiated characteristics such as fenestrations), and regressing (degenerative cell walls with intraluminal stasis) stages of vessel development. Examination of serial sections with three-dimensional reconstruction of specimens from patients with proliferative diabetic retinopathy indicated that new vessels developed by invading extracellular matrix through a process of cytoplasmic extension by an exposed endothelial cell, which was followed by luminal budding.

If one were to postulate that vessels developed in solid cords, endothelial cells would have to migrate and lose their polarity. In our study, solid cords of endothelial cells were not seen, and endothelial cells always maintained polarity (that is, retained a luminal and abluminal side).

Intercellular gaps were not seen in new vessels, and fenestrations were rarely seen in developing or regressing new vessels, although mature vessels demonstrated fenestrations in seven of 23 vascularized membranes. Fenestrations may not be responsible for the bleeding tendency of new vessels. The regressing type of vessel, with its degenerating endothelial cell wall, may contribute to spontaneous hemorrhages in proliferative diabetic retinopathy. In new vessel development there is a continuous process of progression from the developing phase to the regressing phase that begins with endothelial cell cytoplasmic extension and basal lamina fragmentation followed by luminal budding. Next, these vessels mature, developing thinner walls, wider lumina, and a well-formed basal lamina. Finally, endothelial cell cytoplasmic and nuclear architecture degenerates as the vessel enters the regressing phase. When a sufficient number of fragile regressing vessels are present, hemorrhage may occur. This may correlate with the clinical observation that vitreous hemorrhage is not only seen with the first appearance of neovascularization, but also after laser treatment or in later stages of disease when regressing vessels are present.

New vessel formation in diabetic retinopathy closely resembles the observations made in experimental retinal neovascularization in the rabbit and has some significant differences when compared to experimental corneal neovascularization (for example, lack of endothelial cell separations). This observation may be

relevant to the study of neovascularization in diabetes and other retinal vasoproliferative diseases.

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OPHTHALMIC MINIATURE

Everybody knows the arcus of old persons. But nobody understands its physiology. It is not always an index of years. It occurs occasionally in middle life; and it runs, according to the statement of a lady, who shewed it when thirty, in all her family; whose members manifest it in early life. It gives a bland, subdued, and dispassionate expression to the eyes; and, perhaps, is intended by nature for one of those symbols of mature and judicious age, which produce involuntary deference in younger breasts.

Robert Hull, "Cursory Notes" in *The Morbid Eye*
London, Longman, Orme, Brown, Green, and Longman, 1840

Narrow-Band Filtering for Monitoring Low-Amplitude Cone Electroretinograms in Retinitis Pigmentosa

Sten O. L. Andréasson, M.D., Michael A. Sandberg, Ph.D., and Eliot L. Berson, M.D.

Low amplitude (<10 μV) cone electroretinograms, elicited with 30-Hz white flicker from 59 patients with retinitis pigmentosa, were computer-averaged alone or in combination with a narrow-band electronic filter that increases the signal to noise ratio, thereby making it possible to evaluate the electroretinograms of most patients with retinitis pigmentosa. Narrow-band filtering reduced the amplitude of computer-averaged responses by an average of 7%, but the change in amplitude was independent of the size of the unbandpassed response. Narrow-band filtering also allowed measurement of 30-Hz cone responses in patients followed up over an 11- to 15-year period and quantitation of responses of less than 1 μV, which were not detectable with computer averaging alone.

THE EARLIEST STUDIES of the electroretinogram in patients with retinitis pigmentosa, performed with electronic filters that passed responses unattenuated over a frequency bandwidth of several hundred hertz, showed that most patients had responses that were indistinguishable from noise (that is, less than 10 μV in amplitude).[1,2] Narrow-band electronic filters that passed frequencies over a few hertz allowed separation of the retinal responses from noise in some patients who had apparently nondetectable electroretinograms recorded with wide-band filters.[3] Summation of responses with computer averaging and wide-band filters made it possible to quantitate responses as small as 1 μV from patients with retinitis pigmentosa within a few minutes of testing.[4] A narrow-band filter combined with computer averaging extended the lower limit of detectability to 0.05 μV (a 20-fold increase in the signal to noise ratio) so that 90% of an outpatient population with retinitis pigmentosa and visual field diameters greater than 8 degrees had detectable responses.[5]

Although narrow-band electronic filters extend the range of detectability, they would be expected to alter the peak amplitude of responses that were not perfectly sinusoidal. With narrow bandpass filtering only the center frequency is preserved, thereby enhancing the signal-to-noise ratio for responses that are predominantly sinusoidal at that frequency. If the original, unbandpassed signal contains sideband frequencies, these components will be lost through a narrow bandpass filter, potentially altering the amplitude. We, therefore, performed this study to determine whether 30-Hz cone electroretinograms of less than 10 μV from patients with retinitis pigmentosa are significantly altered by initially processing the responses through a bandpass filter. We also used this technique in selected patients to show that narrow-band filtering can be used as an aid in following patients over as much as 15 years and in detecting responses of less than 1 μV in amplitude.

Patients and Methods

We selected 59 patients (aged 13 to 47 years), representing the autosomal dominant, autosomal recessive, X-chromosome-linked, and isolate forms of retinitis pigmentosa in approximately equal numbers, from the files of our institution. All patients had computer-

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From the Berman-Gund Laboratory for the Study of Retinal Degenerations, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston. This study was supported in part by National Eye Institute Center grant P50-EY02014; the Retinitis Pigmentosa Foundation Fighting Blindness, Baltimore; and a grant from the Hajjar family, Boston.

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averaged 30-Hz full-field cone electroretinogram responses between 1.5 and 10 μV in amplitude. These responses had been obtained with a wide-band filter (−3 dB at 2 Hz and 300 Hz) and had been stored on magnetic tape with FM electronics (0 to 312 Hz). These responses, replayed from tape, were attenuated at line frequency with a notch filter and then summed ($N \leq 768$) over a 128-msec time window with a signal averaging computer containing a bipolar artifact reject buffer to eliminate deflections exceeding two to three times the average response amplitude for a given patient; these were designated as "unbandpassed" responses. The same responses, replayed from tape, were also attenuated with a Weinbridge analogue narrow-band filter ($Q = 16$) tuned to 30 Hz before computer averaging for each patient; these were designated as "bandpassed" responses. Q denotes the sharpness of frequency discrimination and equals $f_0/(f_H - f_L)$, where f_0 is the center frequency, f_H is the upper −3-dB cutoff frequency, and f_L is the lower −3-dB cutoff frequency. The −3-dB frequencies were approximately 29 and 31 Hz for the narrow-band filter used in this study. With this narrow-band filter and the recording technique previously described,[5] electroretinogram responses greater than or equal to 0.05 μV could be detected.

For each patient, the percent change in peak amplitude with the filter was normalized by a logarithmic transform for statistical analysis. The mean change in log amplitude for the sample of 59 patients was then compared to zero with a *t*-test for statistical significance. The change in log amplitude was also assessed as a function of log unbandpassed amplitude with linear regression to determine whether the effect of the filter on amplitude depended on the size of the unbandpassed response.

We also selected two additional groups of four patients with different genetic types of retinitis pigmentosa. The first group, consisting of patients aged 8 to 26 years at the initial visit, showed that 30-Hz cone electroretinogram responses can be quantitated with the aid of bandpass filtering after an 11- to 15-year interval, despite substantial losses of cone function over that period of time. The second group, consisting of patients aged 18 to 44 years, showed the usefulness of bandpass filtering in quantitating 30-Hz responses of less than 1 μV that could not be detected with computer averaging alone.

Results

Computer-averaged cone electroretinograms detectable without narrow-band filtering (unbandpassed) and with narrow-band filtering (bandpassed) showed comparability of peak-to-peak amplitudes and implicit times (Fig. 1). The signal-to-noise ratio was improved in the bandpassed responses compared with the unbandpassed responses. The mean ± S.E.M. change in log amplitude after filtering for the 59 patients with retinitis pigmentosa was −0.030 ± 0.005 log unit or −7% (antilog of −0.030) and was significantly different from zero ($P < .001$). The difference between bandpassed and unbandpassed amplitudes did not depend on the size of the unbandpassed response (Fig. 2); the slope of the best-fitting linear regression line was not significantly different from zero.

We measured cone electroretinograms to 30-Hz white light from four patients with retinitis pigmentosa tested initially and 11 to 15 years later without narrow-band filtering and without computer averaging (Fig. 3, left column); at the follow-up time, their responses were nondetectable (<10 μV). However, the latter responses could be quantified with narrow-band filtering and computer averaging (Fig. 3, right column). Implicit times (time intervals between stimulus onset and corresponding response peaks) were comparable over time for each patient when comparing unbandpassed, unaveraged responses to bandpassed, averaged responses obtained 11 to 15 years later.

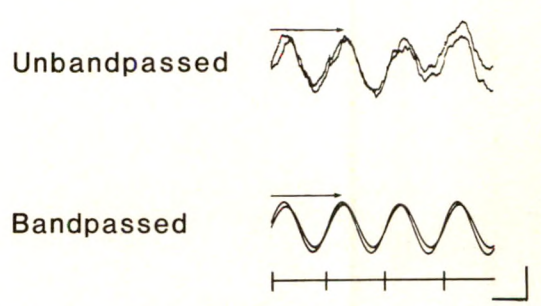


Fig. 1 (Andréasson, Sandberg, and Berson). Computer-averaged (N = 256) 30-Hz full-field cone electroretinograms without and with narrow-band filtering for a patient with retinitis pigmentosa. Stimulus onset, vertical markers; calibration (lower right), 2.0 μV vertically and 20 msec horizontally; arrows designate b-wave implicit times.

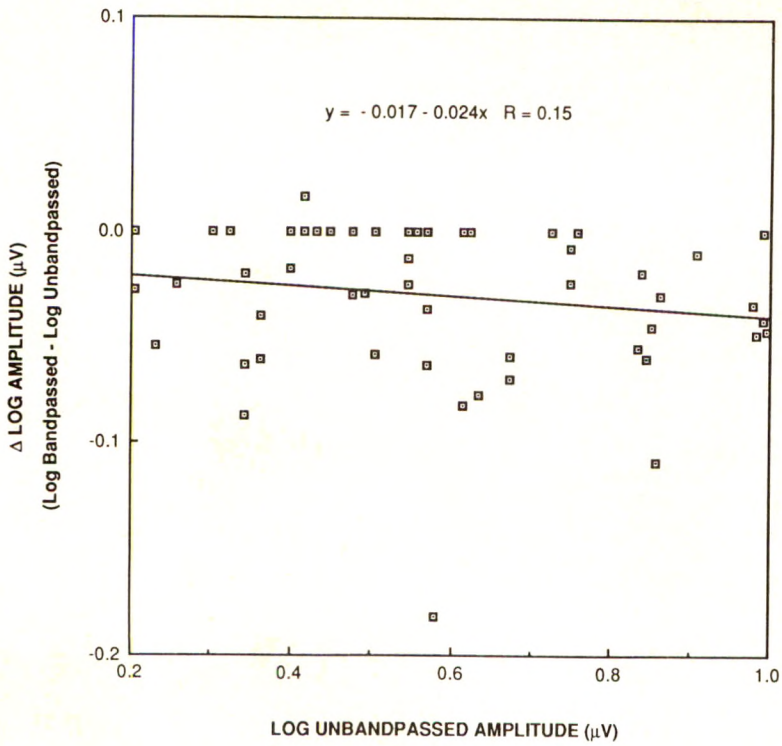


Fig. 2 (Andréasson, Sandberg, and Berson). Change (Δ) in log amplitude (bandpassed minus unbandpassed) as a function of log unbandpassed amplitude for 59 patients with retinitis pigmentosa. Equation describes best-fitting (solid) line, whose slope did not differ significantly from zero ($r = -.15$, $P > .05$).

Computer-averaged, bandpassed 30-Hz electroretinograms from selected patients, representing different genetic types of retinitis pigmentosa whose responses were less than 1 μV, were detectable with narrow-band filtering (Fig. 4). Their responses were reproducible on consecutive runs.

Discussion

The present study shows that narrow-band electronic filtering can aid in monitoring small-amplitude (<10 μV) cone electroretinograms from patients with retinitis pigmentosa and that these responses are not substantially altered in amplitude by this technique. Although narrow-band filtering reduced amplitude an average of 7%, this attenuation with filtering did not depend on the size of the unbandpassed response. Therefore, the percent annual decline in narrow-band filtered 30-Hz cone electroretinogram amplitudes, previously reported in patients with retinitis pigmentosa,[5] would be expected to be the same if the responses could have been monitored with wide-band filtering. In other words, when narrow-band filtering is used to monitor 30-Hz cone electroretinograms in a population of patients with retinitis pigmentosa, responses can be followed over time without concern that the filter itself is modifying the apparent course of the disease.

Selected cases also showed that responses can be quantitated over an 11- to 15-year interval in patients who have lost considerable cone function. Other cases showed that bandpass filtering can increase the range of detectability at least one order of magnitude over computer averaging alone, such that responses less than 1 μV can be quantitated. Since this technique extends the range of detectability and, thereby, the capacity to observe patients with computer averaging over a longer term, we are using bandpass filtering with computer averaging to evaluate remaining cone function in patients with retinitis pigmentosa and amplitudes of less than 10 μV.

Although bandpass filtering can be used to detect computer-averaged 30-Hz cone responses of less than 10 μV where the waveforms appear sinusoidal, this technique should not be used to monitor small-amplitude responses elicited by single flashes of light (0.5 to 1.0 Hz) where the responses are not sinusoidal. It remains to be established whether 30-Hz cone responses of greater than 10 μV in patients

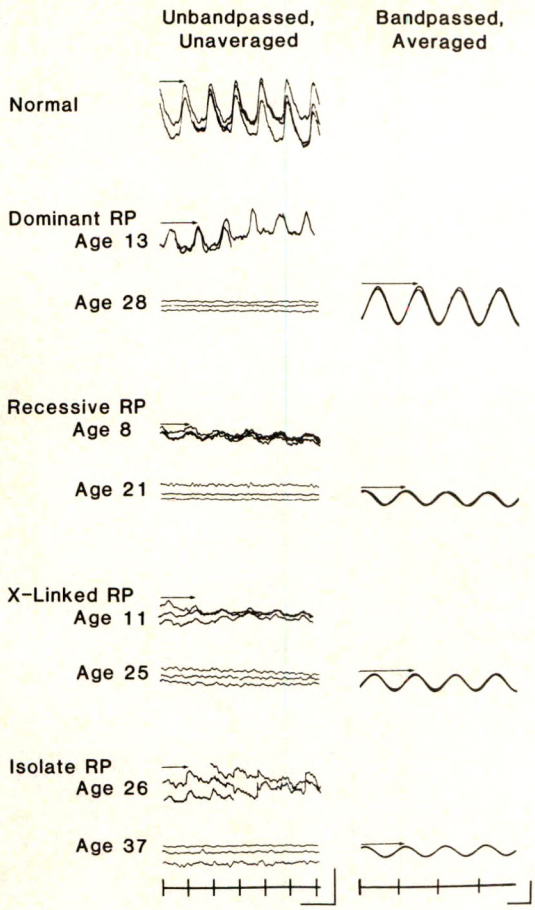


Fig. 3 (Andréasson, Sandberg, and Berson). Full-field 30-Hz electroretinograms from a normal subject and four patients with retinitis pigmentosa tested at an 11- to 15-year interval. Stimulus onset, vertical markers; calibration symbol (left column, lower right) designates 100 μV vertically for the normal subject and top three patients and 40 μV vertically for the bottom patient and 50 msec horizontally for all traces; calibration (right column, lower right) designates 2 μV vertically for the dominant, X-linked, and isolate patients and 0.3 μV for the recessive patient and 20 msec horizontally for all traces. B-wave implicit times are designated with arrows. RP, retinitis pigmentosa.

with different genetic types of retinitis pigmentosa can be bandpassed with only minimal attenuation of amplitude. At present, for patients whose cone electroretinogram responses were initially greater than or equal to 10 μV with wide-band filtering and whose cone responses are now less than 10 μV with narrow-band filtering, we would apply an amplitude correction of +7% to the narrow-band filtered responses to estimate the amount of change over time.

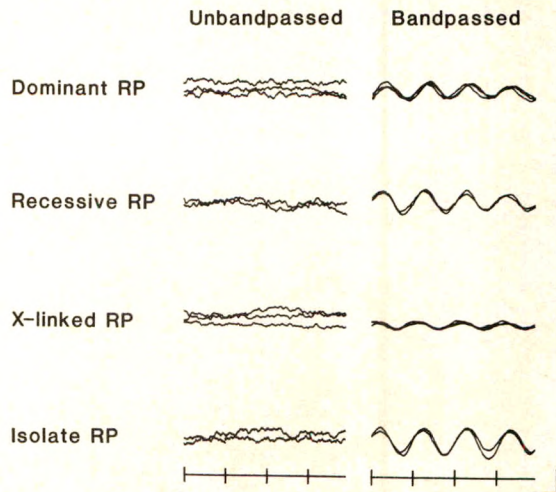


Fig. 4 (Andréasson, Sandberg, and Berson). Computer-averaged (N = 256) 30-Hz full-field electroretinograms monitored without and with narrow-band filtering for four patients (aged 44, 40, 18, and 39 years) with amplitudes of less than 1.0 μV. Stimulus onset, vertical markers; calibration (right column, lower right) is vertically 2.0 μV for traces in the left column and 0.2 μV for traces in the right column and 20 msec horizontally for all traces. RP, retinitis pigmentosa.

With the present techniques of computer averaging and narrow-bandpass filtering, most patients with retinitis pigmentosa and some remaining visual field have a detectable cone electroretinogram response, which constitutes an objective measure of remaining cone function. Detectable responses recorded at one- to two-year intervals can be used to help define the course of the disease.

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Clinical Findings and Common Symptoms in Retinitis Pigmentosa

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Data analysis was performed in a prospective study of clinical symptoms and findings in 500 patients with retinitis pigmentosa. The symptoms and findings in these patients met the usual definitions of the disease. At initial examination the patients were questioned in a standardized manner; symptoms and associated health problems were reviewed. Some patients were unable to answer all of the questions. Of the patients 274 (55%) were men and 226 (45%) were women, with a race distribution of 21 (4%) black, 47 (9%) Hispanic, 26 (5%) Oriental, three (1%) American Indian, and 403 (81%) white.

Sixty-nine patients reported no symptoms of night blindness and 116 patients claimed no visual field changes; 90 stated that they saw better at dusk. The most common problem noted by 263 (53.3%) was headaches, 31 on a daily basis, 42 at least weekly, 124 infrequently, and the remainder nonspecifically. Numbness or tingling, mainly in extremities, was reported by 99 patients. The second most common problem affecting 170 patients (34.6%) was light flashes; since eight patients had retinal detachments, light flashes cannot be totally discounted. Of 143 patients who had been pregnant, 14 had visual changes.

RETINITIS PIGMENTOSA is the name commonly given to a group of disorders characterized over many years by progressive loss of visual field, night blindness, and degeneration of the retina. Patients in this group have a constellation of symptoms that occur less commonly in other types of retinal disease. These symptoms include chronic light flashes, headaches, paresthesias, and vision varying from day to day and under different situations. In order better to understand the occurrence and character of these symptoms, as well as to evaluate common demographic features of our retinitis pigmentosa population, we conducted a prospective study of the historical, clinical, and symptomatic findings of the first 500 patients entered into the computerized data bank of the UCLA Retinitis Pigmentosa Registry. We were also interested in evaluating whether certain symptoms were more common in specific retinitis pigmentosa types as defined by previously reported electroretinographic and psychophysical characteristics.[1,2]

Methods

On the initial visit of every retinitis pigmentosa patient, a comprehensive family history, pedigree, and questionnaire are completed by a UCLA medical genetics counselor in a standardized manner. The first two questions are: "Do you have night blindness, or more difficulty seeing in dimly lighted areas compared to others? For how many years?" and "Have you noticed a loss of peripheral or side vision? For how many years?" In order to classify the type of retinitis pigmentosa, electrophysiologic and psychophysical testing and clinical examination are performed; these results are correlated and analyzed to diagnose as carefully as possible the type of disease, or to group the patients by degenerative mechanism on the basis of the effect on photoreceptors.[2,3]

The questionnaire reviewed the patient's medical and family history, and asked about unusual pregnancy or birth defects such as polydactyly and congenital deafness, and

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whether the patient had headaches, numbness and tingling, and flashes of light. The latter symptoms were specifically characterized if present. Patients were also asked about how they first learned about their retinal problem and what they were told; this information was so variable that it was not quantitated. Patients were asked if there was any factor that made their retinitis pigmentosa worse or better, and if answered positively these factors were characterized. Women were asked whether any pregnancy had made their retinitis pigmentosa worse. Occasionally a patient would decline to answer a question and the space was left blank.

The retinitis pigmentosa type was classified on the basis of a combination of the patient's inheritance pattern, electroretinographic testing, fundus pattern (if distinctive), and the final rod threshold taken from several areas of the retina.[2] Electroretinographic testing was performed in a standardized fashion with a Ganzfeld bowl stimulator, Burian-Allen contact lens electrode, and a protocol that measures the cone-mediated and rod-mediated systems as well as both systems together.[1,2] Generally, if on testing a patient with abnormal peripheral visual fields demonstrates rod function more severely affected than cones, and if both rods and cones are abnormal, the patient is said to have a rod-cone degeneration. Conversely, if the cones are more severely affected and both are abnormal, the patient is said to have a cone-rod degeneration. If a retinitis pigmentosa patient has a nonrecordable single flash response and a visual field greater than 12 degrees, a final rod threshold better than 2.0 log units of elevation after 40 minutes of dark adaptation demonstrates the presence of areas of residual rod function; such a patient probably would have had a cone-rod pattern when the electroretinogram was previously recordable. Studies of retinitis pigmentosa patients with this pattern of loss strongly suggest a progression of the electroretinogram in the cone-rod pattern from recordable to nonrecordable but with measurable residual rod function.[4] This finding is seen consistently in families with autosomal dominant and recessive retinitis pigmentosa cone-rod degeneration.[5] On occasion a patient with a nonrecordable electroretinogram cannot be completely classified in this scheme, since diagnostic clues are unavailable. All retinitis pigmentosa patients with either rod-cone or cone-rod patterns have progressive visual field loss and retinal degeneration.

Patients with congenital deafness were classified into Usher syndrome types I or II on the basis of whether the deafness was total or partial.[6] Polydactyly, body habitus including truncal obesity, mental retardation, and hypogenitalism were used to make the diagnosis of Bardet-Biedl syndrome.[7] Patients with choroideremia were included in this study since they met all the standard definitions of retinitis pigmentosa except for their distinctive fundus appearance. Choroideremia patients are night blind from an early age, with progressive visual field loss and ring scotomas similar to other retinitis pigmentosa types leading to tunnel vision; when the electroretinogram can be recorded, a rod-cone degenerative pattern is seen. Inheritance is in an X-linked chromosome manner.

The term "simplex" is used to denote that no family history of retinitis pigmentosa could be found on extensive questioning of the patient and the mendelian inheritance pattern could not be determined.[8] The term "multiplex" refers to families where one or more siblings are affected but there is no family history outside the sibship of retinitis pigmentosa; while it might be assumed that the mendelian inheritance is autosomal recessive, other possibilities exist and the term multiplex reflects this variability.

Results

The sex distribution of patients studied in the UCLA Retinitis Pigmentosa Registry was 274 (55%) male and 226 (45%) female, similar to that found by Nettleship[9] in a survey of retinitis pigmentosa in Europe in 1907. The race distribution in the Registry in comparison with the populations of California and the United States is provided in Table 1. Of the entire group, 41 were the offspring of consanguineous marriages, with an additional 23 having family histories suggestive that parents might be related. Of 500 patients, six were adopted and 36 had no knowledge of their family history.

Among various types of retinitis pigmentosa, 116 claimed no symptomatic visual field changes even though all patients showed contracted visual fields. For those who noted visual field changes, the mean age of onset was 24.0 years and varied depending on inheritance pattern and primary diagnosis (Table 2).

While night blindness is a well-known fea-

TABLE 1
RETINITIS PIGMENTOSA POPULATION DISTRIBUTED BY RACE*

RACE	UCLA RP REGISTRY	NORMAL (CALIF.)	NORMAL (U.S.A.)
White	81.0%	76.0%	83.0%
Black	4.0%	8.0%	12.0%
Hispanic†	9.0%	19.0%	6.5%
Oriental	5.0%	5.0%	1.5%
American Indian	1.0%	1.0%	0.5%

*Statistical abstracts of the United States 1984; U.S. Department of Commerce, Bureau of the Census.

†This figure includes all persons of Spanish origins and overlaps with other categories.

ture of retinitis pigmentosa, not all patients initially have this symptom; 69 denied any problems with night vision on close questioning, and 90 stated that their vision was better at dusk. For the patients who had night blindness, the mean age of onset was 19.0 years; values varied depending on inheritance pattern and primary diagnosis (Table 3). Patients with rod-cone degeneration have an earlier onset of night blindness than patients with cone-rod degeneration. Choroideremia and Usher syndrome patients, both of which typically have rod-cone degeneration patterns on the electroretinogram, also had early nyctalopia. Patients with cone-rod patterns of degeneration tended to notice their visual field loss less than patients with rod-cone degeneration.

Headaches are not usually thought to be associated with retinitis pigmentosa, yet 263 patients (53.3%) reported headaches on a regular basis, with the pain located behind the eyes in 22, over the eyes in 104, in the temples in 43, in the back of the head in 36, as pins and needles in the eyes in three, and nonspecifically in 55. In terms of frequency, 31 (11.8%) had the headaches on a daily basis, 42 (16.0%) on a weekly basis, 16 (6.1%) on a monthly basis, and 174 (66%) infrequently or nonspecifically.

Light flashes were seen by 170 patients (34.6%) and seem to be associated with more advanced stages of the disease, with 56 (32.9%) stating that they saw them on a daily basis, 19 (11.2%) as a weekly to monthly event. Patients were further able to characterize the flashes, with 112 (22.8%) having rolling waves of light, 48 (42.9%) on a daily basis and 14 (12.5%) on a weekly to monthly basis. Jagged flashes of light were reported by 42 patients (8.5%), eight (19.0%) on a daily basis and two (4.8%) on a weekly to monthly basis.

When patients with headaches were analyzed in terms of the type of light flashes they saw, the following results were found: headaches occurred in 100 patients of 170 reporting light flashes, in 66 patients of 112 reporting rolling waves of light, and in 29 of 42 reporting jags of light. Chi-square analysis suggests no significant difference in the occurrence of headaches with jags, rolls, or flashes of light.

Ninety-nine patients reported sensing numbness and tingling, usually in extremities. Of those who experienced paresthesias, 74 of 99 complained of headaches, 49 experienced light flashes, 30 saw rolls of light, and only 11 saw jags of light. A chi-square analysis suggests that there is no significant difference in the occurrence of numbness and tingling with various light phenomena. Retinal detachment occurred in eight patients, so symptoms of light flashes in retinitis pigmentosa cannot be totally discounted.

Episodes of acute visual loss were identified by 201 patients; 84 claimed stress as the major factor, 17 said that illness was responsible, 24 blamed a combination of stress and illness, and 76 said that other problems had adverse effects.

On a review of systems, 213 of the group complained of suffering from at least one other systemic disorder; these include 103 with deafness (partial or full), 42 with arthritis, 36 with neurologic deficits, 31 with vascular problems, 15 with bone problems, 11 with polydactyly, and 16 with seizures. Sixty-four patients complained of acquired hearing loss but Usher syndrome, in which deafness is congenital, was not diagnosed. Acquired deafness was not studied to see whether incidence in older age in retinitis pigmentosa varies from normal age-matched controls, but a recent study by McDonald, Newsome, and Rintelmann[10] in 45 patients suggests that there may be a higher incidence in the retinitis pigmentosa population that is seen normally as part of aging.

Of the 500 retinitis pigmentosa patients, eight stated that a medication diminished their eyesight, while 28 claimed that some medication improved or stabilized their vision (Table 4). Of patients who became pregnant, 14 of 143 experienced visual changes during pregnancy. Of 83 smokers, only two stated that cigarettes affected their vision.

A number of patients had interesting reports

TABLE 2

ONSET OF SYMPTOMATIC VISUAL FIELD CHANGES IN RETINITIS PIGMENTOSA BY INHERITANCE PATTERN AND CLINICAL DIAGNOSIS

	NO. OF SYMPTOMATIC PATIENTS	MEAN AGE OF ONSET (YRS)	NO. OF ASYMPTOMATIC PATIENTS*
Inheritance pattern			
Autosomal dominant	39	25.13	12
Autosomal dominant with incomplete penetrance	16	21.38	8
Autosomal recessive	53	19.96	13
X-linked recessive	38	15.03	17
Simplex	198	26.78	52
Multiplex	38	23.19	13
Unknown	2	24.00	1
Total	384	—	116
Clinical diagnosis			
Autosomal dominant rod-cone	22	22.13	6
Autosomal recessive rod-cone	15	20.85	3
X-linked recessive rod-cone	18	11.00	5
Simplex rod-cone	46	25.48	10
Multiplex rod-cone	12	20.25	1
Autosomal dominant cone-rod	13	33.33	11
Autosomal recessive cone-rod	6	31.14	3
X-linked recessive cone-rod	3	24.00	4
Simplex cone-rod	51	34.24	18
Multiplex cone-rod	5	20.40	0
Autosomal dominant nonrecordable electroretinogram, visual field <10 deg	4	24.40	1
Autosomal recessive nonrecordable electroretinogram, visual field <10 deg	8	22.00	1
Simplex nonrecordable electroretinogram, visual field <10 deg	29	28.13	6
Multiplex nonrecordable electroretinogram, visual field <10 deg	5	40.75	0
Choroideremia	18	18.44	8
Usher syndrome, Type I	20	15.63	2
Usher syndrome, Type II	19	21.74	7
Preserved para-arteriolar retinal pigment epithelial retinitis pigmentosa	3	7.33	1
Leber's amaurosis congenita	7	<0.50	0
Juvenile onset	13	4.73	2
Autosomal dominant Leber's amaurosis	5	12.20	0
Congenital retinitis pigmentosa with macular coloboma	6	8.10	2
Bardet-Biedl syndrome	6	19.00	2
Retinitis punctata albescens	1	52.00	0
Other secondary retinitis pigmentosa	9	19.33	2
Unknown retinitis pigmentosa type/atypical	16	30.31	9
Pigmented paravenous retinal choroidal atrophy	7	14.00	3
Sector retinitis pigmentosa	7	25.00	6
Goldmann-Favre disease	1	10.00	0
Oxalosis	1	53.00	0
Pericentral retinitis pigmentosa	8	43.50	1
Uniocular pigmentary retinopathy	2	45.00	0
Retinitis pigmentosa inversa	0	00.00	1
Retinitis pigmentosa with Coats' disease	1	44.00	0
Total	384	—	116

*Of those questioned, 23% claimed no visual field changes, even though their visual field was abnormal on testing.

TABLE 3

ONSET OF NIGHT BLINDNESS IN RETINITIS PIGMENTOSA BY INHERITANCE PATTERN AND CLINICAL DIAGNOSIS

	NO. OF SYMPTOMATIC PATIENTS	MEAN AGE OF ONSET (YRS)	NO. OF ASYMPTOMATIC PATIENTS*
Inheritance pattern			
Autosomal dominant	43	18.26	8
Autosomal dominant with incomplete penetrance	20	14.40	4
Autosomal recessive	61	15.67	5
X-linked recessive	45	9.74	10
Simplex	220	22.15	30
Multiplex	40	20.90	11
Unknown	2	8.50	1
Total	431	—	69
Clinical diagnosis			
Autosomal dominant rod-cone	26	10.44	2
Autosomal recessive rod-cone	16	14.06	2
X-linked recessive rod-cone	23	6.78	0
Simplex rod-cone	50	18.59	6
Multiplex rod-cone	13	14.44	0
Autosomal dominant cone-rod	17	25.41	7
Autosomal recessive cone-rod	9	29.88	0
X-linked recessive cone-rod	3	19.00	4
Simplex cone-rod	57	30.02	12
Multiplex cone-rod	3	24.33	2
Autosomal dominant nonrecordable electroretinogram	5	18.80	0
Autosomal recessive nonrecordable electroretinogram	9	18.22	0
Simplex nonrecordable electroretinogram	33	22.44	2
Multiplex nonrecordable electroretinogram	5	30.20	0
Choroideremia	21	11.24	5
Usher syndrome, Type I	19	12.05	3
Usher syndrome, Type II	25	18.04	1
Preserved para-arteriolar retinal pigment epithelial retinitis pigmentosa	4	4.00	0
Leber's amaurosis congenita	7	<0.50	1
Juvenile onset	12	4.47	3
Autosomal dominant Leber's amaurosis	4	8.25	1
Congenital retinitis pigmentosa with macular coloboma	4	12.87	4
Bardet-Biedl syndrome	7	12.00	1
Retinitis punctata albescens	1	56.00	0
Other secondary retinitis pigmentosa	9	13.89	2
Unknown retinitis pigmentosa type/atypical	24	28.12	2
Pigmented paravenous retinal choroidal atrophy	7	18.43	3
Sector retinitis pigmentosa	11	21.27	2
Oxalosis	0	00.00	1
Goldmann-Favre disease	1	10.00	0
Pericentral retinitis pigmentosa	8	35.25	1
Retinitis pigmentosa inversa	1	10.00	0
Retinitis pigmentosa with Coats' disease	1	44.00	0
Total	431	—	69

*A number of patients, even some severely affected, denied night blindness.

TABLE 4
EFFECT OF MEDICATIONS ON RETINITIS PIGMENTOSA REPORTED BY PATIENTS

IMPROVED OR STABILIZED	MADE WORSE
Beta-carotene (3)*	Antidepressant medications
Vitamin A (4)	Eye tests
Vitamin C (2)	Quinidine (2)
Vitamin D	Diet pills (amphetamines)
Vitamin E (4)	Thioridazine (Mellaril)
Encad—Russian treatment	Contraceptive pill
Steroids	Vitamins
Persantine	Pilocarpine 2% eyedrops
Valium	
Placental extract (Switzerland)	
Murocoll #2 eyedrops—scopolamine and Neo-synephrine	
Estrogen	
Niacin	
Direct eye injections (Italy)	
Small white pills	
Penicillin	
Eyedrops	
Sheep liver cells	

*Number in parentheses represents number of patients who reported this finding.

about their experiences with ophthalmologists on learning about the diagnosis of retinitis pigmentosa. Among the common myths or misstatements related to patients by ophthalmologists were that the patient would be blind within a year, and that the patient should buy a white cane or learn Braille. Since retinitis pigmentosa is a chronic disease that spans decades, this type of advice provides a disservice to the patient, and raises unnecessary fears. Any ophthalmologist who predicts a date when the patient will become blind invariably will be incorrect, and since progression is so slow, this type of statement is destructive to the morale of the patient. Mobility training is seldom needed or wanted by patients unless their visual field is less than 3 degrees, although some protection may be afforded by a white cane for crossing roadways.

Many patients were told that their retinitis pigmentosa either came from their mother or that it was a genetic disease, and that they should not have children. Since X-linked inheritance constitutes only about 6% to 8% of the retinitis pigmentosa seen in the United States, it is not justifiable to state that the patient has inherited the retinitis pigmentosa gene from the mother unless there is a clear X-linked pedigree. Pronouncing that the disease is inherited from the mother often raises unnecessary guilt in her, and occasional anger toward her by the patient.

Discussion

Several important aspects of this survey are surprising and important to the retinitis pigmentosa patients. Clearly, a number received misinformation from their ophthalmologist on the duration and effects of these diseases and on the hereditary aspects, particularly on the issue of having children and receiving the retinitis pigmentosa gene from the mother.

Even more hazardous for the ophthalmologist is to give unofficial genetic counseling when the type of retinitis pigmentosa may be unclear. Advising patients on having children involves complicated issues. Theoretically, it is safe for most retinitis pigmentosa patients to have children, since most offspring will be unaffected although many will be carriers of a retinitis pigmentosa gene. Only patients with autosomal dominant inheritance are at immediate risk (about 50%) of having affected children. These issues are difficult and can be effectively handled by skilled counselors in medical genetics.

There is no question that the diagnosis of retinitis pigmentosa is a difficult one for the practitioner to relate, being well aware of the potential severity of the problem and, currently, its incurability. Unfortunately, this difficulty often conveys itself to the patient as reticence to discuss the problem fully and may be interpreted as hostility. Many patients are in a state of shock from the diagnosis, and a follow-up counseling appointment to answer questions is usually helpful. Although there is currently no cure for retinitis pigmentosa the practitioner should continue to see the patient regularly, since most have refractive errors and some will develop cataracts which eventually may need surgery. The practitioner can also relate the availability of ultraviolet screening lenses and antiradical oxygen scavengers such as vitamin E, ascorbic acid, and beta-carotene, which as a general class of dietary agents many researchers believe is helpful in protecting the patient with retinitis pigmentosa or retinal degeneration.[11]

Among the less known symptoms experienced by retinitis pigmentosa patients are light flashes, which appear to occur more frequently in advanced cases. Many patients are reassured when told that other retinitis pigmentosa patients also have light flashes, that they are part of the disease process, and that there is no evidence that they are detrimental. The association of light phenomena with headaches may suggest that a subset of retinitis pigmentosa patients have a migraine variant. Standard headache medications may be used in retinitis pigmentosa patients since there are no known contraindications to these drugs.

Retinal detachment occurred in eight of 500 retinitis pigmentosa patients even though it could have been assumed that pigmented scarring and atrophy typical of retinitis pigmentosa would prevent detachment. Patients who complain of sudden loss of vision should have their eyes dilated and examined for retinal detachment. Although light flashes are common in retinitis pigmentosa, at their first onset a dilated examination may be advisable.

Recognition that many retinitis pigmentosa patients have residual rod function has led to systems in which patients with diffuse rod disease are classified separately from those who show a mixed cone and rod loss but in whom the rods are not diffusely affected.[12,13] These patterns have been shown in retinitis pigmentosa patients on the electroretinogram[1,2,5,14] and have been demonstrated psychophysically.[15,16] In our laboratory, patients with cone-rod patterns on the electroretinogram also have had reasonably good rod function on dark adaptation testing.[4,5] In autosomal dominant and recessive patients the classification of retinitis pigmentosa type on the basis of whether rod function is present has been consistent within family studies. However, inconsistency in the presence of residual rod function has been seen in a large X-linked retinitis pigmentosa pedigree, in which both cone-rod and rod-cone electroretinogram patterns were found.[17] Patients with X-linked retinitis pigmentosa are the only clear exception to the classification by rod function, but autosomal dominant and recessive patients appear to be well classified by these techniques. Cone-rod degeneration patients also have unique visual field changes consisting of ring scotomas closer to fixation, and less sensitivity loss between the edge of field and pericentral areas, often resulting in an onionskin appearance to the isopters, pseudoaltitudinal defects, and enlarged blind spots early in the disease.[6,18]

Reviewing the age of onset of nyctalopia (Table 2) shows that many retinitis pigmentosa patients do not notice night blindness until they are in their 20s or 30s, and when questioned have not noted any particular problems in the dark. They may even deny problems of seeing in the dark but note difficulties in adapting on entering darkened areas or occasionally on going out into sunlight. Because of the insidious nature of the progression, many patients do not realize they have a problem until their central field is affected. If the problem is picked up on routine eye examination, many patients feel they do not have a problem, which is the likely source for the lack of response this study received for questions asking for the date of onset of night blindness or visual field loss.

The distribution of retinitis pigmentosa by race shows no significant difference from overall racial distribution in California or the United States.

Patients commonly reported that stress made their vision worse and when the stress was relieved their vision usually was better. Patients frequently noted variability in their vision, stating clearly that they were having "good" days or "bad" days. Sometimes patients would note that their vision was best early in the morning, stating it was "crystal clear," but that it would deteriorate by late morning. The basis of this finding is not understood. Ross and colleagues[19] measured intervisit variability in visual field testing and found much greater variance in retinitis pigmentosa patients when compared with the control group, which is consistent with the results of our study.

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OPHTHALMIC MINIATURE

For all this, however, Bradley cannot see behind himself. Much of the court and, thus, a good deal of the action are often invisible to a basketball player, so he needs more than good eyesight. He needs to know how to function in the manner of a blind man as well. When, say, four players are massed in the middle of things behind Bradley, and it is inconvenient for him to look around, his hands reach back and his fingers move rapidly from shirt to shirt or hip to hip. He can read the defense as if he were reading Braille.

W. Howarth, Editor, *The John McPhee Reader*
New York, Random House, Inc., 1976

Corneal Infection in Mucosal Scarring Disorders and Sjögren's Syndrome

L. David Ormerod, M.D., Lye P. Fong, M.D., and C. Stephen Foster, M.D.

We reviewed 69 episodes of microbial keratitis occurring over an 11-year period in 56 patients with a mucosal scarring disorder or Sjögren's syndrome. Gram-positive bacterial isolates were the most common cause of infection, and accounted for almost all cases in patients with Sjögren's syndrome. Trichiasis (cicatricial pemphigoid), topical corticosteroids, bandage contact lenses, and corneal surgery were the main predisposing factors in the development of the corneal infection. In patients with ocular cicatricial pemphigoid, infection was much less common after chemotherapeutic control had been achieved. Recurrent infections were relatively frequent. There was a high rate of major complications, particularly in microbial keratitis complicating Sjögren's syndrome.

CICATRIZING DISORDERS of the conjunctiva comprise a complex and heterogeneous group of diseases and include ocular cicatricial pemphigoid, Stevens-Johnson syndrome, atopic keratoconjunctivitis, graft-vs-host disease, alkali burns, and radiation keratitis. They have been classified conventionally as dry eye disorders, irrespective of their origin, although aqueous and mucin tear deficiencies may occur late in their development.[1,2] The term "primary ocular surface disease" has been proposed[1] to differentiate this group by emphasizing the active involvement of both the corneal and conjunctival epithelia. However, the inflammatory events, which are usually immunologically driven, are not localized to the epithelium, and we prefer the term "mucosal scarring disorders." All of these disorders are characterized by a final common pathway of subepithelial fibrosis in the context of chronic inflammation and epithelial perturbation with squamous metaplasia.[1-3]

The normal ocular surface is highly resistant to infection, and bacterial adhesion and proliferation are largely dependent on a break in surface integrity. Despite the frequency of punctate epitheliopathy, filamentary keratopathy, and squamous metaplasia, microbial keratitis is probably a rare complication in the purely aqueous-deficient dry eye. However, microbial keratitis may be much more prevalent in patients with a mucosal scarring disorder[2,4] and in Sjögren's syndrome related to autoimmune lacrimal gland disease.[5,6] Herein we describe the results of our analysis of 69 cases of microbial keratitis occurring in patients with either a mucosal scarring disorder or secondary Sjögren's syndrome.

Material and Methods

We studied retrospectively 69 consecutive episodes of microbial keratitis complicating ocular cicatricial pemphigoid (33 episodes in 28 patients), Stevens-Johnson syndrome (ten episodes in six patients), a miscellaneous group of other mucosal scarring disorders (five patients: two with chronic alkali burn injuries, and one each with graft-vs-host disease [two episodes], atopic keratoconjunctivitis, and radiation keratitis), or Sjögren's syndrome (20 episodes in 17 patients). Sjögren's syndrome was diagnosed by the presence of concurrent rheumatoid ar-

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thritis and keratoconjunctivitis sicca. All patients were treated at our institution between January 1977 and October 1987.

The criterion for inclusion in the study was a hospital discharge diagnosis of microbial (nonviral) keratitis occurring in a patient with one of the above diagnoses. A review of inpatient and outpatient charts was made using a standardized protocol, with emphasis on factors predisposing to corneal infection. Corneal scrapings from all patients had been inoculated onto blood, chocolate, and modified Sabouraud agars and into cooked meat broth, using standard techniques.[7,8] Sabouraud agar was incubated at 25 C and the others at 37 C. Minimal microbiologic criteria were positive cultures on two or more media or on one medium with a corroborative Gram's stain.

Results

There were 43 females and 13 males, with 37 right and 32 left eyes involved. Patients ranged in age from 6 to 91 years. The mean age (±S.E.) of the patients with ocular cicatricial pemphigoid was 68 ± 12 years; Stevens-Johnson syndrome, 24 ± 15 years; the miscellaneous group of mucosal scarring disorders, 32 ± 16 years; and Sjögren's syndrome, 65 ± 14 years. Gram-positive bacterial infections predominated in all groups of patients, but particularly in patients with Sjögren's syndrome (Table 1). Trichiasis was associated in half of the patients with cicatricial pemphigoid. The use of topical corticosteroids and bandage contact lenses as well as structural abnormalities after corneal surgery were generally important potential predispositions for microbial keratitis (Tables 2 and 3).

Most patients with ocular cicatricial pemphigoid at our institution are treated by the Ocular Immunology Service. Our best epidemiologic statistics, therefore, exist for this group. Of 178 patients with ocular cicatricial pemphigoid treated by one of us (C.S.F.) over the 11-year period under study, 17 (10%) developed 18 episodes of microbial keratitis. In three patients, the diagnosis of cicatricial pemphigoid

TABLE 1
CAUSE OF MICROBIAL KERATITIS*

ORGANISM	CICATRICIAL PEMPHIGOID (N = 28)	STEVENS-JOHNSON SYNDROME (N = 10)	MISCELLANEOUS GROUP (N = 6)	SJÖGREN'S SYNDROME (N = 17)
Gram-positive cocci				
Staphylococcus aureus	11	1	2	10
Coagulase-negative staphylococci	5	3	1	4
β-hemolytic streptococci†	3	1	1	2
Viridans streptococci	4	1	—	—
Streptococcus pneumoniae	1	1	—	—
Gram-positive bacilli				
Corynebacterium sp.	1	—	—	—
Bacillus sp.	—	—	—	1
Gram-negative bacilli				
Pseudomonas aeruginosa	1	2	1	1
Klebsiella sp.‡	4	1	—	—
CDC VE-2	1	—	—	—
Proteus sp.§	2	—	—	1
Moraxella sp.	1	—	1	—
Acinetobacter calcoaceticus	2	—	—	—
Haemophilus parainfluenzae	1	—	—	—
Unclassified *Pseudomonas*	—	—	1	—

*All cases were culture positive.

†Two patients with Group A and five patients with Group B.

‡Three patients with *K. pneumoniae* and two patients with *K. oxytoca*.

§Two patients with *P. mirabilis* and one patient with *Morganella morganii*.

TABLE 2
LOCAL OCULAR FACTORS POTENTIALLY PREDISPOSING TO MICROBIAL KERATITIS*

PREDISPOSING FACTORS	CICATRICIAL PEMPHIGOID (N = 33)	STEVENS-JOHNSON SYNDROME (N = 10)	MISCELLANEOUS GROUP (N = 6)	SJÖGREN'S SYNDROME (N = 20)
Topical corticosteroids	9	5	2	11
Bandage contact lens wear	6	6	3	9
Trichiasis	17	1	—	—
Corneal surgery†	5	1	1	4
Corneal glue	1	—	—	3
Lagophthalmos	4	—	1	—
Meibomianitis	4	—	—	—
Staphylococcal blepharitis	—	—	1	4
Recurrent bacterial conjunctivitis	1	—	—	—
Dacryocystitis	1	—	—	—

*N = no. of episodes of microbial keratitis.

†Eleven patients, comprising five lamellar keratoplasties, four penetrating keratoplasties, and two patients shortly after cataract extraction.

was made at admission for microbial keratitis. Infections occurred in three patients within eight weeks of instituting immunosuppressive therapy, in two of 12 patients (three episodes) whose therapeutic control was inadequate, and in two patients whose disease status was uncertain after premature cessation of treatment (dapsone) because of drug toxicity. Corneal infection developed in one patient receiving oral corticosteroids alone[2] and in one of 22 (4%) clinically quiescent, untreated patients. Subtracting these 12 patients, and allowing for the 12 patients with unsuccessful chemotherapy and the 22 patients with inactive disease, microbial keratitis occurred in only five of 144 patients (3%) after full control of disease activity (determined clinically) by immunosuppressive chemotherapy. All five had a major surgical predisposing factor; individual infections were associated with a lamellar keratoplasty, cataract extraction, corneal glue, a bandage contact lens, and lagophthalmos.

Over the same time period, 12 patients with ocular cicatricial pemphigoid attended by other physicians in the Department of Ophthalmology were admitted for 15 episodes of microbial keratitis; 11 of the 12 patients (14 infections) were not receiving systemic immunosuppres-

TABLE 3
USE OF SYSTEMIC IMMUNOSUPPRESSIVE CHEMOTHERAPY CONCURRENT WITH THE ONSET OF MICROBIAL KERATITIS*

IMMUNOSUPPRESSIVE AGENT	CICATRICIAL PEMPHIGOID (N = 16)	STEVENS-JOHNSON SYNDROME (N = 4)	MISCELLANEOUS GROUP (N = 2)	SJÖGREN'S SYNDROME (N = 6)
Oral corticosteroids	10†	—	2	5‡
Cyclophosphamide	8	—	—	3
Azathioprine	4	4	2	—
Dapsone	2	—	—	—
Cyclosporine	2	—	—	—

*N = no. of patients receiving chemotherapeutic drugs.

†Usually at high dosage; ≥ 10 mg/day of prednisone in 13 of 16 patients.

‡Maintenance chemotherapy for rheumatoid disease; ≤ 10 mg/day of prednisone in three of five patients.

sive drugs. The total number of patients with ocular cicatricial pemphigoid treated outside the Immunology Service is unlikely to have been much greater, and it is reasonable to assume that the care of intercurrent external ocular disease would be uniform. Of the 33 cases of microbial keratitis complicating cicatricial pemphigoid, trichiasis in 17 cases (52%), topical corticosteroid use in nine (27%), bandage contact lenses in six (18%), and the inadvertent complications of surgical management in six cases (18%) were the main predisposing causes of corneal infection. Lagophthalmos caused by severe cicatrization was a factor in four patients (12%).

Patients with Stevens-Johnson syndrome had persistent ocular surface problems five months to six years after the primary episode of erythema multiforme. Bandage contact lens (60%) and topical corticosteroid use (50%) were prevalent in this group. Four episodes of microbial keratitis (three in one patient) occurred in two patients being treated with azathioprine for chronic ocular Stevens-Johnson syndrome.[9] The number of patients in the miscellaneous group of mucosal scarring disorders was small, but bandage contact lenses, topical corticosteroid use, and immunosuppressive therapy (for graft-vs-host disease) were prevalent in those who developed microbial keratitis.

Microbial keratitis occurred as an iatrogenic complication more commonly in patients with Sjögren's syndrome than in those with cicatricial pemphigoid or Stevens-Johnson syndrome. Of 20 corneal infections in patients with Sjögren's syndrome, ten (50%) complicated the management of previous sterile ulcerations and six (30%) occurred during treatment for recurrent or chronic epithelial erosions. Topical corticosteroid use and bandage contact lenses were particularly common in these patients (55% and 45%, respectively). The microbial keratitis in patients with Sjögren's syndrome was often slow to resolve with apparently adequate antibiotic therapy.

Recurrent infections were common in all groups. There were five second infections in patients with cicatricial pemphigoid from five months to four years after the initial infection; four occurred in the same eye. All cicatricial pemphigoid patients with recurrent infection had uncontrolled trichiasis. There was no recurrence in patients clinically controlled with chemotherapy. Two patients with Stevens-Johnson syndrome had ipsilateral infections. One patient had three separate infections over a six-year period involving *Pseudomonas aeruginosa* on two occasions (associated first with a bandage contact lens, and then with a penetrating keratoplasty) and *Klebsiella pneumoniae*. Another Stevens-Johnson patient had a bilateral pneumococcal infection complicating bandage contact lens wear. One patient with graft-vs-host disease had separate infections with *P. aeruginosa* and an unclassified *Pseudomonas* in the same eye, four months apart. There were three recurrent infections in patients with Sjögren's syndrome separated by five months to five years; one episode affected the contralateral eye.

Antibiotic therapy generally included round-the-clock[7] topical gentamicin (14 mg/ml) and cefazolin (133 mg/ml). Treatment was varied according to the therapeutic response, and with consideration of the antibiotic sensitivity profile.

Overall, corneal perforation complicated the management of 15 eyes (22%) and a descemetocele (without perforation) of eight eyes (12%) (Table 4). There were three cases of endophthalmitis. Nine eyes were treated with corneal tissue glue and bandage soft contact lenses, and five with bandage contact lenses alone. Five patients with perforation underwent emergency penetrating keratoplasty. Seven patients received a corneal tectonic patch graft, and three received a conjunctival flap. Six eyes (9%) were enucleated. The major complication rate was particularly high in patients with Sjögren's syndrome (50%). Thirteen patients required immediate treatment for trichiasis. During the convalescent period, six patients required a tarsorrhaphy, and two patients underwent punctal occlusions.

TABLE 4
MAJOR COMPLICATIONS OF MICROBIAL KERATITIS*

COMPLICATION	CICATRICIAL PEMPHIGOID (N = 33)	STEVENS-JOHNSON SYNDROME (N = 10)	MISCELLANEOUS GROUP (N = 6)	SJÖGREN'S SYNDROME (N = 20)
Corneal perforation	4	1	2	8
Endophthalmitis†	2	—	—	1
Intact descemetocele	3	3	—	2

*N = no. of episodes of microbial keratitis.

†Cases of endophthalmitis also included in the figures for corneal perforation.

Discussion

Our data suggest a high predisposition to surface infection in patients with mucosal scarring disorders and Sjögren's syndrome. The bacterial spectrum in the patients with cicatricial pemphigoid was somewhat more heterogeneous than in the other groups: staphylococci were the commonest isolates, but a variety of gram-negative bacillary infections were involved in 33% of the culture-positive cases. *Pseudomonas aeruginosa* keratitis was uncommon. The small number of patients in the Stevens-Johnson and miscellaneous groups prevents firm conclusions as to their respective microbial spectra.

In Sjögren's syndrome, staphylococci or streptococci were involved almost exclusively, suggesting a principal role of endogenous bacteria from the conjunctival or adnexal flora. Although studies involving patients with moderately severe dry eye have suggested that the conjunctival flora is relatively normal,[4,10] the flora of patients with severe ocular surface disease has not been investigated formally. An increased systemic susceptibility to staphylococcal infection in Sjögren's syndrome has been reported.[11]

We did find a relatively high rate of occurrence of infection with Group B β-hemolytic streptococci (five of 61 culture-positive infections), suggesting there may be an ecologic niche for this organism in the compromised ocular surface. Group B streptococci are usually rare causes of adult infection.

Impairment of the ocular immunologic defense mechanisms may be an important pathogenetic factor.[12,13] Deficiencies in tear lysozyme, lactoferrin, and IgA[10,13,14] present an enhanced risk of infection to patients with keratoconjunctivitis sicca in general. Long-term antibiotic therapy is often started for this reason. However, despite the persistent presence of punctate erosions of the corneal epithelium, a recent study suggests that microbial keratitis occurs rarely in mild to moderately severe cases of keratoconjunctivitis sicca.[4] The secondary transudation of serum factors may be an important compensatory mechanism.[4,10,13,14] There is evidence that the level of antibacterial proteins in tears may be low in patients with Sjögren's syndrome and relatively normal in many patients with ocular cicatricial pemphigoid.[14]

Qualitative differences in the ocular surface are difficult to assess. Although the mucosal scarring disorders share many clinical features with aqueous tear-deficiency syndromes, the former involve fundamentally different and immunologically driven disease processes. Inflammatory mediators (including several eicosanoids) at high concentrations have been detected in the tears of patients with cicatricial pemphigoid.[2] Their potential significance in the abnormal epithelial transdifferentiation,[3,15] increased basal epithelial mitosis, epithelial disruption, glycocalyx instability, and abnormalities of surface mucus[16] remains unknown. Ultimately, tear physiology is severely affected.[17] Advanced squamous metaplasia may itself enhance bacterial adherence to the corneal surface.[18]

The Immunology Service at our institution manages most cases of ocular cicatricial pemphigoid, primarily with systemic chemotherapy.[2,19] Excluding patients in whom therapeutic control was inadequate, only five of 144 patients (3%) developed microbial keratitis more than eight weeks after beginning their immunosuppressive therapeutic regimen, a point at which the pemphigoid inflammatory process usually is controlled.[2] All five had major complicating factors. Although chemotherapy usually was continued for many months and often years, corneal infection was rare if the active mucosal disease was controlled satisfactorily. Foster and associates[2,20,21] have shown that the surface ultrastructural abnormalities in cicatricial pemphigoid revert to normal surface specializations after chemotherapeutic modulation and that cicatricial progression can be prevented. The high incidence of infection in the few patients being treated with conventional (topical) therapy is additional evidence[2,19-21] in support of using immunosuppressive agents to control ocular cicatricial pemphigoid.[2] Only 15% (five of 33) of the episodes of corneal infection occurred in patients satisfactorily controlled with chemotherapy.

The superimposition of additional risk factors on already compromised corneas seems to have been particularly critical in the generation of infection. The long-term use of topical corticosteroid was probably important in the occurrence of microbial keratitis in nine of 33 patients (27%) with cicatricial pemphigoid, seven of ten patients (70%) with Stevens-Johnson syndrome, and 11 of 20 individuals (55%) with Sjögren's syndrome. Topical corticosteroids are ineffective in controlling the disease process in these disorders, and it is prudent to limit corti-

costeroid use to specific indications and for measured intervals only.[2] Topical corticosteroids are particularly hazardous in patients with Sjögren's syndrome; not only do our data suggest an enhanced risk of bacterial keratitis, but corticosteroids have a well-known predilection in Sjögren's syndrome to induce insidious, sterile corneal ulceration and perforation.[22,23]

Ocular toxicity caused by the tear content of chemotherapeutic agents used systemically in doses appropriate to cancer chemotherapy is common,[24,25] but it is unlikely to occur at the relatively modest dosages used for the control of ocular cicatricial pemphigoid or chronic Stevens-Johnson syndrome.[2,8,19] These eyes are quiet and usually asymptomatic during successful chemotherapy. Because a significant danger is engendered by the greater susceptibility of the compromised ocular surface to local drug toxicity, particularly from preservatives,[26] we strongly advise using preservative-free preparations in these patients.[2]

Aberrant eyelashes can be an important cause of epithelial disturbance, persistent epithelial defect, and bacterial surface inoculation, notably in cicatricial pemphigoid. Mechanical epilation is rarely sufficient; eyelash regrowth is rapid, and the short, regrowing eyelash is more traumatic to the ocular surface than the original, long eyelash. Attempts at permanent eyelash ablation should continue until long-term control is achieved. Eyelid margin cryoablation with a 40-second freeze-thaw-refreeze procedure using a nitrous oxide trichiasis cryoprobe is preferred,[2,27,28] after 2% lidocaine (with epinephrine) eyelid infiltration. Meibomianitis is frequently severe in this group of diseases[2] and may itself produce dry eye problems.[29] Systemic treatment for meibomianitis with a tetracycline is commonly required.[18] Permanent punctal occlusion may be necessary to preserve aqueous tears in Sjögren's syndrome and in the advanced stages of the mucosal scarring disorders.[2,30]

Therapeutic soft contact lenses can be useful for managing persistent epithelial defects, but at an increased risk of inducing corneal infection, principally with endogenous organisms.[31] There were 24 episodes of bandage contact lens-associated infections, 15 (63%) of which were associated with topical corticosteroid use. Keratitis with bandage contact lens use was especially frequent in patients with Stevens-Johnson syndrome (60%) and Sjögren's syndrome (45%). All but four of the 22 culture-positive cases associated with the use of bandage contact lenses involved gram-positive organisms.

It is unclear whether prophylactic antibiotics are effective in reducing infections of the compromised ocular surface. However, our study suggests their relative inefficacy. Preinfection antibiotics were used in 46% of the cicatricial pemphigoid cases, 60% of the Stevens-Johnson cases, and 60% of the Sjögren's syndrome cases. Long-term antibiotic use may inhibit the normal ocular flora, which is important in preventing colonization by pathogenic strains, and overgrowth of resistant strains of bacteria may be induced. The impaired ocular surface is also more susceptible to local toxicity from long-term antibiotic use. Topical antibiotics probably should be used for limited intervals only.

The management of microbial keratitis in patients with ocular surface compromise presents formidable medical and surgical challenges. The delivery of adequate topical antibiotics may be more difficult in a cicatrized conjunctival sac, although frequent applications of antibiotic ointments may be useful. Subconjunctival antibiotics should not be used in the mucosal scarring disorders, if possible, to avoid the risk of increasing conjunctival scarring. Healing of the microbial keratitis is generally satisfactory, but can sometimes be prolonged, notably in patients with Sjögren's syndrome. The alarmingly high rate of stromal ulceration with descemetocele/perforation occurring in 50% of the patients with Sjögren's syndrome complicated by corneal infection points to unresolved difficulties in managing the ocular complications of this disease.

In patients with mucosal scarring disorders and Sjögren's syndrome, it is necessary to deal preventively with numerous provocative pathologic and iatrogenic factors; trichiasis control, topical corticosteroid use, and maintaining epithelial integrity are particularly important. Our data suggest that the best way to prevent microbial keratitis in ocular cicatricial pemphigoid is to control chemotherapeutically the immunologically driven inflammatory activity.

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Presumed Autoimmune Corneal Endotheliopathy

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I reviewed 20 previously published cases of presumed autoimmune corneal endotheliopathy. The disease appeared clinically with stromal edema and a slowly migrating line of keratic precipitates. All patients had acute stromal edema and keratic precipitates, and decreased visual acuity. Anterior chamber cells were noted in 11 patients. Inflammatory processes, such as pars planitis and iritis, and intraocular lens implantation were present in 13 patients.

IMMUNOLOGIC REPORTS have previously described the cornea as a site of immunologic privilege.[1,2] Experience with a large population of corneal graft rejection patients, however, has led to a reassessment of the cornea's privileged status.[3] Discovery and enumeration of major histocompatibility and corneal-specific antigens have confirmed the immunogenicity of the cornea,[4,5] while anatomic studies have shown the peripheral cornea to be connected to the immune system via capillary arcades and extension of subconjunctival lymphatics.[6] The central cornea, however, still retains many of the characteristics of privilege, in that it has no vascular or lymphatic connections and is largely devoid of dendritic cells.[7]

The concept of an immunologically privileged site is intriguing for many reasons. Therapeutically, privileged sites possess great potential as transplantation sites; for example, the brain has been used successfully as a recipient site for pancreatic islet cells, as well as adrenal tissue.[8] Conversely, privileged anatomic sites are interesting for their predisposition to autoimmune reactions. Since privileged sites are secluded from immunologic defenses, it may be assumed that they possess antigens that were never learned as self during ontologic development. For example, autoimmune reactions have been demonstrated against sperm.[9] If the cornea is truly a privileged site, one might expect the existence of an autoimmune, autorejection corneal disease. In 1982, Khodadoust and Attarzadeh[10] described just such a disease, which they called presumed autoimmune corneal endotheliopathy. In their study, Khodadoust and Attarzadeh[10] described two men, aged 19 and 58 years, who had bilateral decreased vision and clouding of the cornea. Clinical examination showed corneal stromal edema that progressed from the periphery to the center of the cornea, with a slowly moving line of keratic precipitates preceding the edema. Results of an anterior chamber tap identified lymphocytes and macrophages. The clinical course of these patients so closely paralleled the classic description of corneal allograft rejection[11] that autoimmunity was proposed as a cause for the disease. The disease was bilateral and responded promptly to corticosteroid therapy, giving further evidence of the autoimmune nature of this process. Both patients were nonsyphilitic and had no history of herpetic lesions. Syphilis is important to rule out because it can cause a similar condition, keratitis linearis migrans, that appears as a slowly migrating deep stromal line of keratic precipitates.[12]

Later in 1982, Sugar and Smith[13] described a 65-year-old woman who, three months after cataract extraction with intraocular lens implantation, developed a linear pigmented endothelial line that progressed centrally from the superior corneoscleral rim. This patient, however, did not respond well to corticosteroid therapy and removal of the intraocular lens was necessary. Khodadoust[14] proposed that in this case the intraocular lens was causing a nonspecific inflammatory response that set the stage for an afferent or efferent pathway of immune response, similar to the response seen with nonspecific inflammation in allograft rejection. In 1985, Rice, Tuberville, and Wood[15] reported three similar cases of unilateral linear keratic

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precipitates associated with uncomplicated cataract extraction and intraocular lens implantation. Both intracapsular and extracapsular surgery were involved. Three different types of lenses were implanted: an anterior chamber lens, a posterior chamber lens, and a pupillary-supported lens. Corticosteroid therapy failed in all three cases.

In 1985, Ohashi and associates[16] described two men, aged 29 and 35 years, with progressing bullous keratopathy preceded by a line of keratic precipitates resembling a rejection line. Like Sugar and Smith's patient, these patients did not respond well to corticosteroid treatment. In an attempt to exclude a viral origin for this disease process, culture samples were taken from the aqueous humor and aqueous-antibody titers were performed for herpes simplex, varicella zoster, and measles. The cultures showed no growth and the results of the titers were in the normal range.

In 1984, Sutcliffe and Baum[17] described seven patients with clinical findings similar to those of Khodadoust and Attarzadeh's[10] original patients. Their patients had acute corneal stromal edema with no history of surgery, trauma, ocular disease, or known exposure to noxious agents. Although these seven patients had stromal edema, minimal anterior chamber reaction, and keratic precipitates, the keratic precipitates did not progress in a linear pattern. In three of the patients herpes simplex keratouveitis was present, but apparently only secondary to the corticosteroid therapy; in one patient a diagnosis of acute iridocyclitis was made. Some question exists, therefore, as to whether the disease described by Khodadoust and Attarzadeh accurately describes the patients observed by Sutcliffe and Baum. Sutcliffe and Baum used their own terminology and diagnosed acute idiopathic endotheliitis in their patients with acute stromal edema, minimal anterior chamber reaction, and nonlinearly arranged keratic precipitates. They proposed that inflammation compromises the pump mechanism of the endothelium and induces a chemotaxis, which in turn causes the edema and keratic precipitate formation.

In 1985, Kuljaca and Momirov[18] described a 23-year-old man, who was similar to the patients described by Sutcliffe and Baum, with localized stromal edema and nonlinear fine keratic precipitates. He responded well to topical corticosteroids, but a recurrence was noted three months later. Culture for herpes simplex virus and aqueous-antibody titers were negative.

In 1986, Khodadoust and associates[19] reported an association between presumed autoimmune corneal endotheliopathy and pars planitis, a disease that is characterized by severe vitreous opacities and heavy exudate deposits that overlie the vitreous base, anterior retina, and pars plana. Of ten patients with pars planitis, four had corneal changes consistent with presumed autoimmune corneal endotheliopathy. Two of the patients were seen during the peak activity of pars planitis, and both had stromal edema preceded by distinct linear keratic precipitates. Because of the rarity of autoimmune endotheliopathy, the authors concluded that the association with pars planitis was not coincidental. They also found that both processes involve an immunologic reaction against an avascular tissue (the cornea and the vitreous) and an inflammation of adjacent vascular tissue. They concluded that "any inflammatory process in avascular tissue of an unknown cause that starts from its adjacent vascularized portion is an autoimmune process, until it can be proven otherwise."[19]

Discussion

Since 1982, 20 cases of acute stromal edema and keratic precipitates of unknown cause have been reported (Table 1). Twelve of the patients had linear keratic precipitates advancing from the peripheral cornea in a manner identical to an allograft rejection, while the other eight had keratic precipitates that were not arranged linearly. The dissimilarity could be simply an idiosyncratic variability of immune response or a result of observation at different stages of the

TABLE 1
CLINICAL SIGNS OF PRESUMED AUTOIMMUNE CORNEAL ENDOTHELIOPATHY
(N = 20)

CLINICAL SIGNS	NO. OF CASES
Visual acuity loss	20
Stromal edema	20
Linear keratic precipitates	12
Cells in the anterior chamber	
2+	4
1+	5
Rare	2
Increased intraocular pressure	4
Bilateral involvement	7

TABLE 2
DISEASE PROCESSES ASSOCIATED WITH PRESUMED AUTOIMMUNE CORNEAL ENDOTHELIOPATHY
(N = 20)

ASSOCIATED FACTORS	NO. OF CASES
Implantation of intraocular lens	4
Pars planitis	4
Iritis	5
Secondary herpetic keratitis	3
Response to corticosteroids	13

disease process or the cases presented could represent more than one disease process. In addition to the association with pars planitis, corneal endotheliopathy was closely linked to several other disease processes as well (Table 2). Persistent iritis was described by Rice and colleagues[15] in the patients who had first received intraocular lens implantation, whereas the herpetic keratitis was reported only as a secondary complication of corticosteroid treatment.[17]

With only 20 cases reported in the literature, presumed autoimmune corneal endotheliopathy is admittedly a rare condition. However, it may be more common than currently believed since many cases of idiopathic or postoperative corneal edema are treated with and promptly respond to corticosteroids. Presumed autoimmune corneal endotheliopathy deserves study because of its theoretical as well as its practical implications. As an example of an autoimmune disease directed against a privileged site, presumed autoimmune corneal endotheliopathy likely involves mechanisms similar to other presumed autoimmune diseases of privileged sites (for example, multiple sclerosis, autoimmune male infertility).[8,20] An understanding of presumed autoimmune corneal endotheliopathy may also help explain how and when the immune system learns self antigens. Zak and Linsenmayer[21] reported that specific corneal epithelial antigens appear around day 12 or 13 of gestation. Specific corneal endothelial antigens have not been described, but if they exist their gestational date of origin would probably occur after the 12th week, when the endothelium forms from migrating neural crest cells.[22] Much debate exists as to when the learning of self antigens is completed. Dwyer and McKay[23] reported that by the 12th week of gestation the immune system can mount a specific response. Thus, corneal endothelial-specific antigens may appear on the cell surface at a time after the host has learned its self antigens. Because of the cornea's privileged status, the immune system would have little contact with these foreign antigens and only under unusual circumstances, such as corneal vascularization or chronic inflammation of the anterior chamber, would sufficient exposure occur.

Alternative explanations include that presumed autoimmune corneal endotheliopathy is caused by an autoimmune process caused by cross-reactivity of endothelial antigens and viral antigens or other exogenous antigens (for example, allergies), or that it is an immune response to virally infected endothelial cells. In presumed autoimmune corneal endotheliopathy, as well as in many other autoimmune diseases suspected of viral origin, isolation of the virus has proven difficult. However, because of the technical problems encountered in culturing viruses, investigators have been reluctant to deny the possibility of a viral origin.

An in vitro model for studying autologous responses to whole corneas would help in determining whether or not the adult cornea possesses antigens recognizable as foreign. In initial experiments in the rat, it has been determined that lymphocytes cocultured with autologous irradiated corneas are stimulated to proliferate significantly more than controls (unpublished data). Orthotopic, autologous corneal grafts showing graft rejection, however, would be the ideal animal model of presumed autoimmune corneal endotheliopathy. Autologous corneal rejection would require the stimulated expression of corneal-specific antigens normally unseen or sequestered from the immune system.

The search for an origin of presumed autoimmune corneal endotheliopathy will result in more than just the pathophysiologic description of another disease. Understanding the immunologic characteristics of this autoimmune disease promises potential ramifications in the fields of transplantation and autoimmunity.

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OPHTHALMIC MINIATURE

The question will be asked why more people cannot see fairies. . . . The answer is that almost nobody tries after they are grown up . . . and the few who know that fairies exist do not always try to see them in the right way. While angels are almost never seen with the physical eye, fairies can be seen in that way, especially out of the corner of the eye. The theory is that the central part of the retina is used so much for ordinary sight that it does not respond to the more delicate vibrations of light from fairies, whereas the rest of the retina is fresh and more suitable for such uses.

Dora Van Gelder, *The Real World of Fairies*
The Theological Publishing House, 1977

Vitamin A Eyedrops for Superior Limbic Keratoconjunctivitis

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We treated 12 patients with superior limbic keratoconjunctivitis with topical vitamin A (retinol palmitate) eyedrops. After a follow-up period of at least three months, this therapy was found to be effective, to a varying extent, in ten patients (83%). Superior limbic keratoconjunctivitis lesions did not recur in these patients as long as topical application was continued.

SUPERIOR LIMBIC KERATOCONJUNCTIVITIS manifests with intractable, chronic inflammation of the superior limbic area of the bulbar conjunctiva. It occurs predominantly in middle-aged women, with persistent irritative ocular symptoms. Although superior limbic keratoconjunctivitis has been recognized as a relatively common disease since first described by Theodore in 1963,[1] the exact cause remains unknown. A variety of modes of therapy, including topical application of silver nitrate solution,[2,3] recession or resection of the bulbar conjunctival lesion,[4-6] or pressure eye patching followed by soft contact lens wearing,[7] have been reported as effective to varying degrees. Recently, thermocauterization has also been proven beneficial as an alternative treatment for superior limbic keratoconjunctivitis.[8]

We herein report on an essentially new mode of therapy for superior limbic keratoconjunctivitis: topical application of vitamin A eyedrops.

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Patients and Methods

There were 11 women and one man in this study, ranging in age from 37 to 68 years, who fulfilled the criteria of superior limbic keratoconjunctivitis on initial examination (Table). The duration of disease varied from one month to 20 years. Keratoconjunctivitis sicca was noted in five patients (Patients 1, 2, 3, 5, and 7). Three patients (Patients 4, 11, and 12) had hyperthyroidism. Seven patients (Patients 1, 2, 4, 5, 6, 10, and 11) had been unsuccessfully treated with topical corticosteroids. The lesions in two patients (Patients 1 and 2) had failed to respond to repeated applications of silver nitrate solution.

Chronic conjunctivitis of unknown cause had been diagnosed in most patients before visiting our clinic.

After obtaining informed consent, the patients were instructed to instill vitamin A eyedrops four times a day. The vitamin A solution used contained either 500 or 1,500 IU/ml of retinol palmitate dissolved in borate buffer (pH 5.3), with low amounts of detergent. This preparation was proven via high-performance liquid chromatography to remain stable for at least six months at room temperature, if kept unopened.

To evaluate the efficacy of the treatment, disease severity was graded into four categories according to the following criteria: grade 3 lesions showed superior limbal ridge or corneal filaments, or both, localized injection of the bulbar conjunctiva, and positive rose bengal staining; grade 2 lesions showed the latter two findings; grade 1 lesions showed positive rose bengal staining alone; and grade 0 lesions showed none of the above findings.

The patients were examined every two weeks during the first two months of therapy and every month thereafter. Either 500 IU/ml (VA-5) or 1,500 IU/ml (VA-15) of vitamin A eyedrop

TABLE
CLINICAL PROFILES OF PATIENTS WITH SUPERIOR LIMBIC KERATOCONJUNCTIVITIS
(N = 12)

PATIENT NO., AGE (YRS), SEX	DURATION OF DISEASE	PREVIOUS TREATMENT*	KERATOCONJUNCTIVITIS SICCA	THYROID FUNCTION	GRADE OF LESION BEFORE/AFTER VA THERAPY†	THERAPY	RESPONSE TO THERAPY	FOLLOW-UP PERIOD (MOS)
1, 68, M	20 yrs	TCS, SN	Yes	Normal	3/1	VA-5/VA-15	Yes	24
2, 50, F	1 yr	TCS, SN	Yes	Normal	3/0–1	VA-5/VA-15	Yes	14
3, 49, F	3 yrs	None	Yes	Normal	3/0–1	VA-15	Yes	23
4, 45, F	1 mo	TCS	No	Increased	3/1	VA-15	Yes	5
5, 48, F	5 yrs	TCS	Yes	Normal	3/1	VA-5/VA-15	Yes	8
6, 41, F	15 yrs	TCS	No	Normal	3/2–3	VA-15	No	14
7, 41, F	4 yrs	None	Yes	Normal	3/1	VA-15	Yes	10
8, 42, F	2 yrs	None	No	Normal	2/1	VA-15	Yes	13
9, 36, F	2 mos	None	No	Normal	3/3	VA-5/VA-15	No	12
10, 55, F	3 mos	TCS	No	Normal	3/1	VA-5	Yes	3
11, 56, F	20 yrs	TCS	No	Increased	3/1	VA-15	Yes	6
12, 44, F	1 mo	None	No	Increased	3/1	VA-15	Yes	3

*TCS, topical corticosteroids; SN, silver nitrate application.
†See text for grading scale of superior limbic keratoconjunctivitis.

solution was given. If the patient did not respond well to VA-5 during a period of at least one month, the therapy was generally changed to VA-15. All the patients included in this study were followed up for at least three months after initiating the topical vitamin A therapy. Of the 12 patients, five initially received VA-5 and seven received VA-15.

Results

Of the five patients given VA-5, only one (Patient 6) showed a favorable response. In this patient the multiple corneal filaments disappeared and the degree of rose bengal staining was dramatically reduced in two months. In the other four patients, although the treatment was changed to topical VA-15 after one or two months, their symptoms had been greatly alleviated during topical application of VA-5. Three of these four patients, after being given topical VA-15, started to show gradual improvement within the next two months. Three months after initiating VA-15 therapy, the superior limbic keratoconjunctivitis lesions became much less inflamed and keratinized, although a slight degree of rose bengal staining remained. In one patient (Patient 7), however, a three-month application of VA-15 was ineffective.

Six of the seven patients who were initially given topical VA-15 also showed varied degrees of improvement within three months. Topical VA-15 therapy was unsuccessful in one patient in this group (Patient 9).

The overall efficacy of topical vitamin A therapy was about 83% (ten of 12 patients). In nine patients, the lesions improved by a score of two or more grades. One patient improved by one grade and two patients showed no substantial improvement. Therapy was generally continued after the superior limbic keratoconjunctivitis lesion had almost disappeared; the lesions did not recur during the follow-up period. Topical VA-5 or VA-15 did not seem to be toxic to the external eye, although some patients complained of slight irritation on instillation.

Case Reports

Case 1

This 68-year-old man had suffered from persistent irritation of his left eye for over 20 years. Based on the diagnosis of keratoconjunctivitis sicca, he had been treated with a variety of surface lubricants, with unsuccessful results. At first examination, on Feb. 25, 1985, a lesion typical of superior limbic keratoconjunctivitis

(sectorial injection of the upper bulbar conjunctiva, superior limbal ridge, and corneal filaments) was found in his left eye (grade 3 severity). There was a moderate papillary response at the tarsal conjunctiva, associated with a slight to moderate degree of hypolacrimation. The findings in his right eye were also suggestive of superior limbic keratoconjunctivitis, but were much less prominent. Thyroid function was normal.

Based on the diagnosis of superior limbic keratoconjunctivitis, he was treated with multiple applications of topical sliver nitrate solution during the next two months. Although his symptoms were temporarily relieved after each treatment, this approach was ultimately unsuccessful. At this point, we discontinued silver nitrate therapy and began treatment with topical VA-5 four times a day. The lesion remained essentially unchanged for the next month, despite a slight lessening of symptoms (Fig. 1, left). Therapy was then changed to topical VA-15 four times a day. One month later, his symptoms had drastically improved. Hyperemia of the bulbar conjunctiva and superior limbal ridge was reduced in severity and the corneal filaments had completely disappeared (grade 0 to 1 severity) (Fig. 1, right). He has applied topical VA-15 for almost two years since this time, with no significant exacerbation of symptoms.

Case 12

This 44-year-old woman noticed a foreign body sensation in both eyes one month before visiting our clinic. Chronic conjunctivitis had been diagnosed by her local physician, and she was unsuccessfully treated with topical applications of ocular lubricant and antibiotics. She was referred to our clinic on Oct. 22, 1986. Biomicroscopy showed that the superior upper bulbar conjunctiva was hyperemic, with intense rose bengal staining. A superior limbal ridge had formed in the right eye (grade 3 severity) (Fig. 2, left). There was a moderate papillary response in the tarsal conjunctiva and the tear meniscus was of normal height. She had been treated for hyperthyroidism for ten years.

Based on the diagnosis of superior limbic keratoconjunctivitis, topical VA-15 four times a day was initiated. Within one month the superior limbal ridge had diminished, and the superior bulbar conjunctiva had become less inflamed and stained minimally with rose bengal dye (grade 1 severity) (Fig. 2, right). Topical VA-15 therapy was continued without exacerbation of symptoms over the next two months.

Discussion

Despite the relatively early recognition of superior limbic keratoconjunctivitis, its pathogenesis remains obscure. Several pathogenetic mechanisms, including autoimmune disorder,[9] atypical trachoma, and the mechanical rubbing theory,[10] have been proposed to explain its origin.

Conversely, histopathologic studies have invariably provided evidence of keratinization of the bulbar conjunctival epithelium with some inflammatory reaction.[4,11,12] It is well known that vitamin A can reverse keratinization[13,14]; therefore, irrespective of whether or not keratinization itself could be a primary abnormality in superior limbic keratoconjunctivitis, this led us to consider the use of topically applied vitamin A to resolve this condition. Recently, the use of topical vitamin A therapy against a variety of keratinizing ocular disorders has been reported with encouraging results.[15,16]

In the present study, topical vitamin A therapy, using retinol palmitate solution, was effective in treating superior limbic keratoconjunctivitis. The overall efficacy of this therapy (83%) was not as good as that with pressure patching and a therapeutic soft contact lens (100%),[7] but was nearly comparable to that with thermocauterization (73%)[8] or conjunctival resection (80%).[5,6] Although there have been no strictly established data concerning the efficacy of silver nitrate treatment, topical vitamin A therapy seemed to give better results since, in our experience, the silver nitrate treatment has generally required repeated applications, with only transient relief of symptoms. Two patients in the present study whose symptoms resisted silver nitrate application responded well to topical vitamin A therapy. Once remission was achieved, the disease did not recur as long as the therapy was continued.

The mechanisms by which vitamin A eyedrops resolved the superior limbic keratoconjunctivitis are unclear. One attractive hypothesis is that vitamin A is locally deficient in patients with superior limbic keratoconjunctivitis. Recently, Ubels and colleagues[17,18] demonstrated that the tear film serves as an important delivery route for vitamin A to the ocular surface epithelium. If so, disturbance of vita-

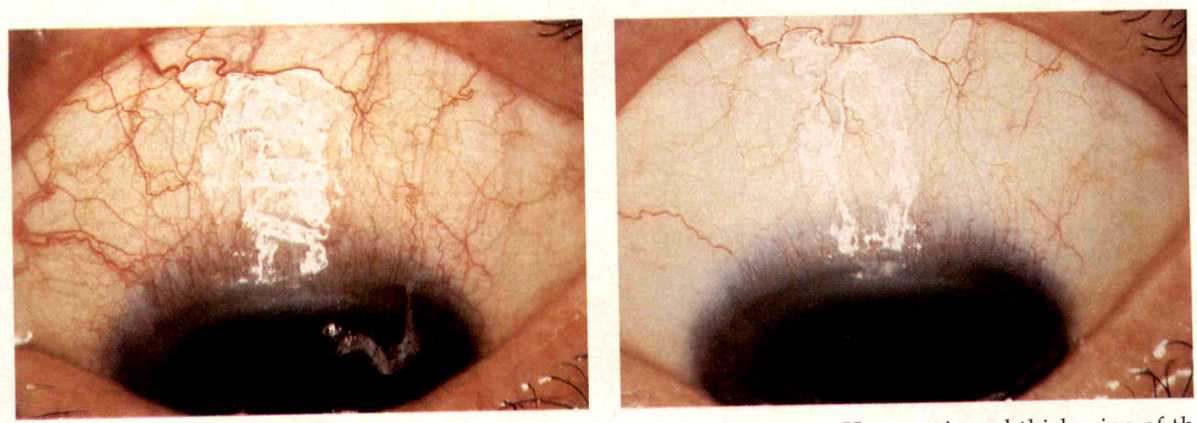


Fig. 1 (Ohashi and associates). Case 1. Left, Before topical VA-15 therapy. Hyperemia and thickening of the superior bulbar conjunctiva are still prominent. Several corneal filaments were seen at the superior portion of the cornea. Right, One month after topical VA-15 therapy. The superior limbic area is of nearly normal appearance.

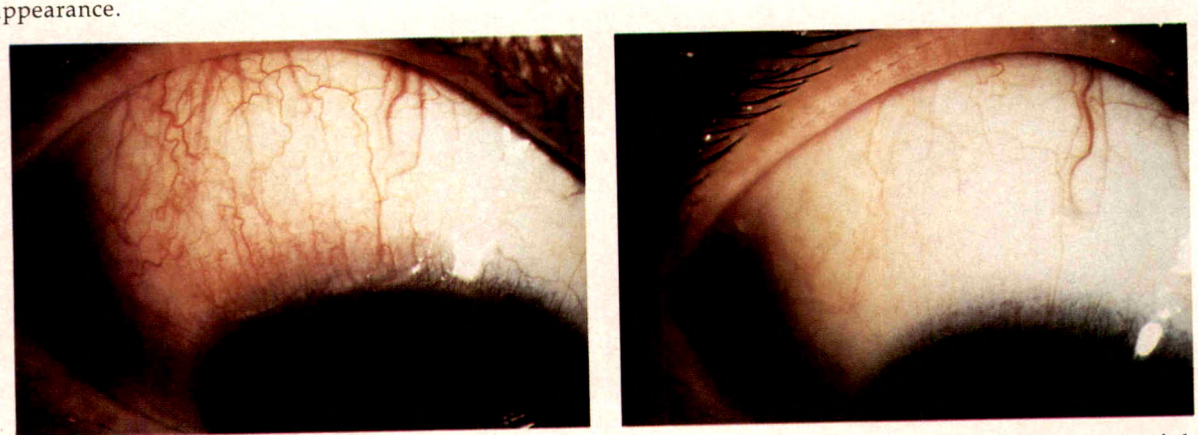


Fig. 2 (Ohashi and associates). Case 12. Left, Before topical VA-15 therapy. Note marked hyperemia of the superior bulbar conjunctiva along with formation of a superior limbal ridge. Right, Two months after topical VA-15 therapy. The lesion at the superior limbic area has cleared up, with minimal staining by rose bengal dye.

min A supply to the tears could be a significant factor in initiating this disease. The high association of keratoconjunctivitis sicca with superior limbic keratoconjunctivitis patients in our study, as has also been emphasized in previous reports,[7,8] might partly support this theory. Another possibility is that topically applied vitamin A may stimulate synthesis by the epithelium of glycoproteins, which modulate the keratinization process, as shown in previous studies.[19,20]

To our knowledge, this is the first topical mode of therapy against superior limbic keratoconjunctivitis. We believe that this therapy should be considered before any surgical therapy is undertaken. In view of the weaker antikeratinizing activity of retinol palmitate as compared with those of synthetic retinoids,[13] our preparation is of limited efficacy in treating superior limbic keratoconjunctivitis. The introduction of a synthetic retinoid for treating superior limbic keratoconjunctivitis, therefore, would certainly be beneficial.

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Ophthalmic miniature

The horny substance of the corneal tunic is lined by a serous membrane; and covered by a mucous, or some modification of a mucous, coat. And if the inflammation be, therefore, deep, it is to be attacked with systematic remedies; the local not neglected. Such a disorder should be treated with mercury or turpentine conveyed into the stomach; and antimonial eruption produced on the side of the head. This part must be shaved; and the smooth portion of the temples, unhairy by nature, should be religiously avoided, on account of the unseemly scars left by the antimonial pustules. I have seen the bosom of a handsome lady quite disfigured by these cicatrices; antimony having been rubbed upon that region for a pleurisy. I have seen the throat of a finely-formed, beautiful young woman equally damaged by this remedy, applied against bronchocele.

Robert Hull, "Cursory Notes" in *The Morbid Eye*
London, Longman, Orme, Brown, Green, and Longman, 1840

An HLA-D Region Restriction Fragment Associated With Refractory Behçet's Disease

Jiro Numaga, M.D., Kazumasa Matsuki, M.D., Manabu Mochizuki, M.D., Mutsuhiko Minami, M.D., and Takeo Juji, M.D.

We examined the association between HLA-DQ and refractory Behçet's disease at the genomic DNA level. Using a restriction endonuclease *Taq* I and a DQβ cDNA probe, we identified the 1.9 kb DQβ restriction endonuclease fragment tightly associated with refractory Behçet's disease. This observation indicates that genomic HLA-DQ variations affect the development of refractory Behçet's disease.

BEHÇET'S DISEASE is a systemic disorder of recurrent inflammation.[1,2] The symptoms include oral and genital ulcerations, skin eruptions resembling erythema nodosum, hyperirritability of the skin, hypopyon iritis, posterior uveitis, and arthritis. Uveitis is among the most deteriorating symptoms and, if untreated, leads to visual loss in most patients.[2] Although colchicine and immunosuppressants, like cyclophosphamide, are usually effective in treating the uveitis, there is a small subgroup of patients for whom the disease is refractory to such treatments.[3,4] They have recurrent ocular attacks and tend to lose their eyesight rapidly even under optimal therapy.

The strong association between Behçet's disease and the human leukocyte antigen (HLA) B51 is well known.[5,6] More than half of Japanese patients with Behçet's disease are HLA-B51 positive.[5-7] This strong association has been documented in other countries as well.[8,9] However, its association with HLA-D region antigens has not been well established.

The HLA-D region antigens are composed of at least three different groups of molecules: DP, DQ, and DR.[10] These molecules are composed of a dimer of a heavy chain (33 to 35 kDa) and a light chain (27 to 29 kDa). Both heavy and light chains comprise two extracellular domains, a hydrophobic transmembrane portion and a hydrophilic cytoplasmic portion.

Within the HLA-DQ locus, three allelic variations, DQw1, DQw2, and DQw3, are acknowledged officially by the HLA Nomenclature Committee.[10] However, a number of studies indicate the existence of more than three allelic variations within the DQ locus.[11-14] These variations have been demonstrated by serologic studies using alloantisera and monoclonal antibodies and by molecular genetic studies. For example, a murine monoclonal antibody TA10 can divide DQw3 into two subspecificities.[15] Because TA10-defined DQw3 subspecificities correspond completely to genomic and polypeptide DQw3β chain polymorphisms, Kim and associates[16] called TA10-positive cells DQ3.1 and TA10-negative cells DQ3.2. DQw1 and DQw2 are also implicated to split further into fine subspecificities.[11,12,17] Additionally, an alloantiserum TK2 and a monoclonal antibody HU46 may define yet another DQ specificity; TK2 and HU46 react with the DQ blank cells that do not express any of the known three DQ antigens.[18] Recent studies showed that many HLA-associated diseases may actually be more closely related to these fine DQ specificities rather than DR variations.[19-21]

HLA-disease associations are currently being investigated at the DNA level. As compared to conventional serologic methods, DNA analysis

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has several advantages. First, serologic HLA typing is not always possible when the patient is under therapy. Corticosteroid and cytotoxic drugs can reduce the number and viability of peripheral lymphocytes of the patients and may cause false or ambiguous typing results. DNA analysis is possible as long as a sufficient number of viable cells are obtained. Second, serologic HLA typing may not be possible at all laboratories. Preparation of the large battery of HLA-typing sera requires extensive screening of alloantisera, a panel of HLA-typed subjects ready to donate their blood, and international standardization of the typing sera. DNA analysis can be performed without these difficulties. Finally, while serologic studies generally detect antigenic polymorphisms located at the extracellular portion of the HLA proteins, the DNA analysis detects both antigenic and nonantigenic polymorphisms at other parts of the HLA genes as well.

In previous studies, we demonstrated that the refractory form of Behçet's disease is tightly associated with HLA-DQw3, while other forms are not.[22,23] In this study, we examined the restriction fragment length polymorphism in refractory Behçet's disease using a restriction endonuclease *Taq* I and a DQβ cDNA probe. We now identify a strong association between the disease and HLA at the genomic level.

Material and Methods

We included in this study 23 unrelated Japanese patients with refractory Behçet's disease.[22] All of the patients met the diagnostic criteria for Behçet's disease proposed by the Behçet's Disease Research Committee of Japan.[1] All patients with refractory Behçet's disease also had frequent (more than four times per year) attacks of chorioretinitis involving the posterior poles of the eyes and were unresponsive to the conventional treatments, that is, the frequency and severity of the ocular attacks did not respond to colchicine or cyclophosphamide. These patients have all been described previously.[22,23] Twenty-eight randomly selected, unrelated healthy Japanese subjects served as controls.

Serologic HLA typing—A modified two-stage complement-dependent microcytotoxicity method was used for HLA typing.[24] For typing fine DQ specificities, murine monoclonal antibodies TA10, HU46, and a human alloantiserum TK2 were used in addition to standard anti-DQ antisera. TA10 defines a variant of the DQw3 antigen.[15] Herein we refer to DQw3- and TA10-positive cells as DQ3.1, and DQw3-positive and TA10-negative cells as DQ3.2, according to Kim and associates.[16] TK2 and HU46 define a new DQ specificity corresponding to the DQ blank phenotype that is unreactive to other known anti-DQ antisera.[18] Herein we refer to TK2- and HU46-positive cells as DQWa.[18]

Restriction fragment length polymorphism analysis—Peripheral blood was drawn after informed consent was obtained. Genomic DNA was isolated by the methods described by Maniatis, Fritsch, and Sambrook.[25] The DNA samples were digested with *Taq* I (Takara Shuzo Co., Osaka) according to the manufacturer's specifications. Digested DNA (8 to 12 μg) was electrophoresed on a 0.7% agarose gel and transferred to nylon membranes, by the method of Southern.[26] The filters were prehybridized overnight at 42 C in bags containing 50% deionized formamide, 5× Denhardt's solution (0.1% bovine serum albumin, 0.1% Ficoll type 400, 0.1% polyvinylpyrrolidone 40), 5× SSPE (0.9 M NaCl, 5 mM edetic acid, 50 mM sodium phosphate buffer, pH 7.4), 1% sodium dodecyl sulfate, 5% dextran sulfate, and 200 μg/ml sheared, denatured salmon sperm DNA. They were then hybridized with the ^{32}P-labeled cDNA DQβ probe[27] (labeled by the random hexamer priming method[28] to 2 to 4 × 10^8 cpm/m/g specific activity) for 40 hours at 42 C in the same buffer as that used for prehybridization. Filters were washed twice at room temperature for five minutes in 2× SSC (1× SSC: 150 mM NaCl, 15 mM sodium citrate); twice at 65 C for 30 minutes in 2× SSC, 0.5% sodium dodecyl sulfate; and once at 65 C for 30 minutes in 0.1× SSC. Filters were dried and exposed to Kodak X-Omat AR films for two to five days at −70 C using Dupont Lighting Plus intensifying screens.

Results

In the restriction fragment length polymorphism pattern of the patient DNA hybridized to the DQβ cDNA probe, all except two patients (lanes 8 and 23) generated the 1.9 kb fragment

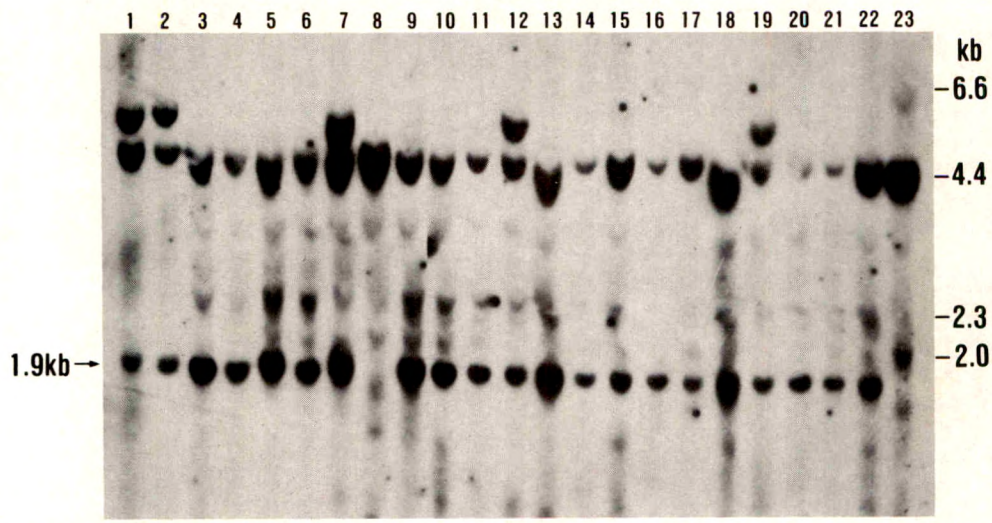


Figure (Numaga and associates). *Taq* I-digested genomic DNA from patients with refractory Behçet's disease hybridized to a DQβ cDNA probe. *Hind* III-digested fragments of bacteriophage lambda DNA was used for a molecular weight marker. The number above each lane corresponds to the patient number in the Table. Only Patients 8 and 23 lacked the 1.9 kb fragment.

(Figure). All 16 DQ3.2-positive patients generated the 1.9 kb fragment (Table). Additionally, five DQ3.2-negative, DQWa-positive patients generated the 1.9 kb fragment. The two patients who did not generate the 1.9 kb fragment were both DQ3.2 and DQWa negative. In the control subjects, 13 DQ3.2-positive and four DQWa-positive subjects generated the 1.9 kb fragment. The remaining 11 DQ3.2-negative, DQWa-negative subjects did not generate the 1.9 kb fragment. The frequency of the 1.9 kb *Taq* I fragments in the patients was 91%, while in the controls it was 61% ($P = .001$ by Fisher's exact test). Consequently, the relative risk[24] of developing refractory Behçet's disease is 13 times greater in the presence of this fragment than in its absence.

Discussion

This study demonstrates that the 1.9 kb *Taq* I DQβ fragment is strongly associated with refractory Behçet's disease. To our knowledge, this is the first study to demonstrate a strong association between Behçet's disease and HLA-D region specificity at the genomic level.

Recent studies demonstrated that the 1.9 kb *Taq* I DQβ fragment is associated with specific DQw3 haplotypes. Using a number of restriction enzymes and homozygous cell lines, Holbeck and coworkers[29] demonstrated the presence of at least two allelic DQβ variants on DQw3-positive, DR4-positive haplotypes. Later, Kim and associates[16] demonstrated the same allelism in DQw3-positive, DR4-negative haplotypes. They designated these variants DQ3.1 and DQ3.2.[16] Cells with DQ3.2 variation generate the 1.9 kb *Taq* I fragment, while cells with DQ3.1 do not. These genomic variations can also be detected as antigenic and electrophoretic differences in the protein products of the genes.[16] Cells with the DQ3.1 variation react to a murine monoclonal antibody TA10, while cells with DQ3.2 do not.[16] They also demonstrated that the specific DQ3.2 restriction endonuclease sites (including the *Taq* I sites) are conserved among many different DQ3.2 cells.[29] Gregersen and colleagues[30] demonstrated that the sequences of the DQβ genes derived from four different DQw3.2-positive cell lines are identical. These observations indicate that the 1.9 kb *Taq* I fragment can be used as one of the genomic markers for the DQ3.2 haplotype. If this is the case, the haplotype highly associated with refractory Behçet's disease is most likely the DQ3.2 haplotype.

However, it should be noted that in this study this 1.9 kb fragment was also observed in five DQw3.2-negative, DQWa-positive patients. The 1.9 kb fragment was also observed

TABLE
HLA-DR AND DQ SPECIFICITIES AND THE 1.9 kb *TAQ* I FRAGMENT IN THE STUDY PATIENTS

PATIENT NO.	HLA-DR	HLA-DQ*	1.9 kb *TAQ* I FRAGMENT†
1	w8, w13	3.2, 1	+
2	w9, w14	3.2, 1	+
3	4, —	Wa, —	+
4	w8, w9	3.2, —	+
5	4, w9	3.2, Wa	+
6	w9, w13	3.2, 1	+
7	w8, w14	Wa, 1	+
8	w11, w14	3.1, 1	–
9	4, —	3.2, Wa	+
10	w9, w8	3.2, —	+
11	4, w9	3.2, Wa	+
12	w8, w13	1, Wa	+
13	4, w9	3.2, Wa	+
14	4, —	3.2, Wa	+
15	w9, w12	3.1, 3.2	+
16	4, w9	3.2, Wa	+
17	2, w8	1, Wa	+
18	w9, —	3.2, —	+
19	w9, w13	3.2, 1	+
20	4, w9	3.2, —	+
21	4, w8	3.2, Wa	+
22	4, w12	3.1, Wa	+
23	2, w8	1, —	–

*DQ3.1, DQw3 positive and TA10 positive; DQ3.2, DQw3 positive and TA10 negative; DQWa, TK2 and HU46 positive, corresponding to the DQ blank specificity.

†+, positive; –, negative.

in four normal DQWa-positive subjects. These findings indicate that the DQWa haplotype also generates the 1.9 kb *Taq* I fragment. The 1.9 kb *Taq* I fragment from the DQ3.2 haplotype includes exons that encode the second extracellular domain and the transmembrane portion of the DQ proteins.[27] Since the sequences encoding these portions are generally better conserved among different haplotypes than those encoding the first extracellular domain,[30] the sequences encoding these and adjacent portions may be similar between the DQ3.2 and the DQWa haplotypes. One possibility is that these portions may actually participate in regulating the disease susceptibility.

Another possibility is that the DQ3.2 and DQWa genes share a common ancestral origin. Recent studies indicate that restriction maps of HLA genes reflect the evolutionary lineages of the genes rather than randomly accumulated mutations.[31] Different HLA genes of close evolutionary origins often generate the same restriction fragment length polymorphism patterns.[14,31] We may postulate a common ancestor to the DQ3.2 and DQWa genes that was in strong linkage disequilibrium with the susceptibility gene to refractory Behçet's disease. The linkage would have remained after the ancestral DQ gene diverted to the DQ3.2 and DQWa genes. In either case, the DNA analysis would help to dissect the disease susceptibility haplotype, and finally to locate the DNA sequences that are responsible for the development of refractory Behçet's disease.

The present study confirmed that active and refractory Behçet's disease is firmly associated with polymorphic DQβ gene variations. A number of data suggest that the HLA-DQ molecules are the products of the immune response or immune suppression genes.[32-36] These genes determine the ability of an individual to generate T cell-dependent immune responses against specific antigens.[37] Polymorphisms in these genes result in genetically controlled differences in T cell-dependent immune response.[32-37] The present study suggests that the disease activity and response to immunosuppressive therapy of an individual with a certain disease may also be genetically determined, at least in part, by their immune response gene variations.

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OPHTHALMIC MINIATURE

I know an albino gentleman who is now well stricken in years, in whom the photophobic distress remains as great, as when he was an infant. Yet his vision, under the adapted degree of light, is as perfect as usual at his advanced years. Two sons of this gentleman display the same total absence of black pigment as does their sire. The father has laboured hard in a vocation which requires an unremitting use of the eyesight; through which he has acquired a lordly fortune. And who would have imagined, a priori, that all this could have been effected, with a daily intolerance of light, by eyes not a whit the worse for sixty years of wear?

Robert Hull, "Cursory Notes" in *The Morbid Eye*
London, Longman, Orme, Brown, Green, and Longman, 1840

Bilateral Anterior Uveitis and Interstitial Nephritis

James T. Rosenbaum, M.D.

Five patients had bilateral anterior uveitis associated with renal disease. Interstitial nephritis was histologically confirmed in three cases. Fatigue, anorexia, abdominal pain, weight loss, and anemia were common systemic complaints or findings. In each case, the uveitis was anterior, eventually bilateral, and associated with minimal visual impairment. Complications of the uveitis included increased intraocular pressure, synechiae, keratic precipitates, macular edema, and intraretinal hemorrhage as well as cells in the anterior vitreous humor and an exudate over the pars plana. Sjögren's syndrome, systemic lupus erythematosus, sarcoid, and syphilis were excluded as diagnoses that could explain the association of renal and uveal disease.

INTERSTITIAL NEPHRITIS is an uncommon renal disease that may occur as a reaction to medications such as antibiotics[1] or noncorticosteroidal anti-inflammatory drugs.[2] An association between anterior uveitis and interstitial nephritis has been previously reported.[3-11] The patients are usually female,[4] and the disease is more common in children than adults.[4] The uveitis may follow, precede, or occur concomitantly with the renal disease.[4] The largest reported series of adult patients with this association included only two patients.[5] To my knowledge, this disease has yet to be described in the ophthalmic literature.

At my institution, patients referred to the uveitis clinic are routinely examined by an internist. From September 1985 (when the clinic opened) through December 1987, five patients had bilateral anterior uveitis in association with interstitial nephritis. The nephritis was proven by biopsy in three patients and clinically suspected in two others.

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Patients and Methods

The patient population at the uveitis clinic is described elsewhere.[12] In brief, the clinic is under the direction of a rheumatologist. Patients are referred for differential diagnosis, treatment recommendations, or patient desire for a second opinion. Many patients are referred with diseases apparently confined to the eye, such as herpes simplex keratouveitis, Fuchs' heterochromic cyclitis, pars planitis, and toxoplasmosis. At this writing, 244 patients have been examined. Virtually all patients were referred by ophthalmologists. Most patients are from the Pacific Northwest region of the United States.

Case Reports

Case 1

Two years before examination, this 43-year-old woman developed a febrile illness associated with flank pain, nausea, and weight loss. She was treated with a cephalosporin for a presumed diagnosis of pyelonephritis. Sterile pyuria, however, was documented after completion of the antibiotic therapy and results of a renal biopsy showed interstitial nephritis. She was treated with a course of oral prednisone at an initial dose of 60 mg/day. Her serum creatinine level rose to slightly over 3 mg/dl, but stabilized at 1.3 mg/dl after corticosteroid therapy. Seven months after onset of the renal disease, she began to experience flashes of green light. An ophthalmologist made a diagnosis of a bilateral iritis. Cystoid macular edema was documented by fluorescein angiography. The patient did well on topical corticosteroid therapy. Two months before examination in the uveitis clinic, however, she began to experience momentary losses of vision affecting only the nasal portion of the visual field of

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the left eye. Ten such episodes, each lasting approximately 30 seconds, occurred over a two-month period. During this period she developed left facial numbness, which lasted one week, and an associated loss of taste over the left half of her tongue as well as left hand and foot numbness. Results of a computed tomographic head scan with contrast performed at this time were normal.

The ocular examination at the uveitis clinic was performed while the patient was receiving 15 mg/day of prednisone orally along with a topical corticosteroid eyedrop. Visual acuity was 20/20 bilaterally, with pinhole improvement to 20/15. Intraocular pressure by applanation was R.E.: 16 mm Hg and L.E.: 27 mm Hg. A rare cell was present in the right anterior chamber. Scattered peripheral intraretinal hemorrhages were present in the temporal portion of the left fundus. Schirmer's testing after instillation of a topical anesthetic showed 2 mm of wetting on the right after one minute and no wetting on the left. The remainder of the examination was unremarkable.

Results of laboratory studies obtained before referral showed mild anemia, a negative fluorescent treponemal antibody test, a negative antinuclear antibody and rheumatoid factor test, a normal angiotensin converting enzyme level and gallium scan, a negative purified protein derivative skin test and a positive reaction to a control antigen, and negative tests for hepatitis B surface antigen and anticardiolipin antibodies. The sedimentation rate was slightly increased. No immunoglobulin deposition was seen in the renal biopsy specimen by immunofluorescence. Carotid ultrasound and echocardiogram did not show a potential source for emboli. A minor salivary gland biopsy showed no focal areas of mononuclear cell infiltration. The momentary visual losses were attributed to a presumed retinal vasculitis.

Case 2

A 13-year-old boy had several months of fatigue and malaise before developing nausea, anorexia, and abdominal pain. On initial examination by a physician, his creatinine level was slightly increased; over the next several days it rose to approximately 5 mg/dl. A percutaneous renal biopsy specimen showed interstitial nephritis with negative immunofluorescence studies. He was treated with prednisone at an initial dose of 60 mg/day. His renal function improved immediately. However, he continued to experience some fatigue, his hematocrit level remained at approximately 30%, and he complained of arthralgias. About three months after the renal disease was diagnosed, the right eye became red; one week later the left eye was similarly affected. A modest amount of pain was initially associated with the ocular disease. The patient responded well to topical corticosteroid eyedrops. He had no complaints suggestive of xerostomia or xerophthalmia.

On examination in the uveitis clinic, visual acuity was R.E.: 20/30, with pinhole improvement to 20/15, and L.E.: 20/20. Nongranulomatous keratic precipitates were present inferiorly over the corneal endothelium bilaterally. Trace to 1+ cells were present in each anterior chamber. A posterior synechia was noted on the right. A Schirmer's test after instillation of a topical anesthetic showed no wetting bilaterally after one minute. Results of the remainder of the examination, including the intraocular pressure, lenses, and fundi, were normal. Results of laboratory studies included a negative antinuclear antibody test and transient eosinophilia. The patient refused a minor salivary gland biopsy.

Case 3

A 42-year-old woman with the recent onset of headaches treated by aspirin or ibuprofen began to experience fatigue approximately 10 months before examination in the uveitis clinic. At that time her creatinine level was 2.6 mg/dl. Over the next several weeks it rose to 9.1 mg/dl. A percutaneous renal biopsy specimen was obtained, which demonstrated interstitial nephritis. The patient was given oral prednisone; her renal function improved and the creatinine level stabilized at 1.3 mg/dl.

The patient's ocular disease began three months after the renal disease was diagnosed, while she was still taking oral corticosteroids. She experienced photophobia in the left eye. A diagnosis of iritis was made and the disease responded to topical corticosteroids. Several weeks later an episode of redness in the left eye was diagnosed as conjunctivitis. Three months before examination in the uveitis clinic, she developed bilateral iritis. On examination in the uveitis clinic, visual acuity was 20/20 bilaterally. Posterior synechiae were present in the left eye and 1+ to 2+ cells were present in both anterior chambers. Cells were also present bilaterally in the anterior vitreous and a white exudate, similar to that seen with typical pars planitis (intermediate uveitis), was present bilaterally over the inferior pars plana. Results of the remainder of the examination, including intraocular pressure, tear formation as judged

by Schirmer's test, optic disks, vessels, and maculae, were normal.

Results of laboratory studies included a hematocrit ranging from 24% to 29%, a negative antinuclear antibody test and serologic study for syphilis, and an increased erythrocyte sedimentation rate. Results of the chest x-ray were normal.

Case 4

A 54-year-old woman developed a presumed ear and throat infection one year before examination in the uveitis clinic. She was treated with a variety of antibiotics, but a low-grade fever persisted. She then developed pyuria, which was attributed to a urinary tract infection, and abdominal pains, which were attributed to gallbladder disease. Recurrent sterile pyuria was documented. Results of an intravenous pyelogram were normal. Five months after onset of the upper respiratory symptoms, the patient noted bilateral ocular redness, discomfort, and photophobia. A diagnosis of iritis was made and the patient was treated with topical corticosteroid eyedrops. The disease improved on therapy but recurred when the medications were tapered. Systemically she felt fatigued, but otherwise was well.

On examination in the uveitis clinic, visual acuity was 20/20 bilaterally. Up to 1+ cells and flare were present bilaterally in the anterior chambers and a few cells were present in the anterior vitreous. Results of the remainder of the examination, including Schirmer's testing, intraocular pressure, and ophthalmoscopy with dilated pupils, were unremarkable.

Results of laboratory studies included a hemoglobin level as low as 9.8 g/dl, an eosinophil count as high as 10% with a white blood count of 6,500/mm^3, a creatinine level of 1.4 mg/dl, a normal chest x-ray, and negative tests for antinuclear antibodies and rheumatoid factor. The erythrocyte sedimentation rate was normal, but the immunoglobulin level was slightly increased on electrophoresis. The patient was HLA-B27 negative.

Comment—Although only a borderline increase in her serum creatinine level was documented, this patient's sterile pyuria, anemia, fatigue, and abdominal pain are otherwise typical of the syndrome of uveitis associated with interstitial nephritis.

Case 5

A 52-year-old man was seen four weeks after the onset of a systemic illness characterized by headache, arthralgias, fatigue, night sweats, fever to 102 F, transient right hand numbness and weakness, anorexia, weight loss, nausea, and inguinal and axillary adenopathy. Shortly after the onset of the illness, his eyes became red and he complained of photophobia and foggy vision. Ocular symptoms were diminished by topical corticosteroid eyedrops.

On examination in the uveitis clinic, visual acuity was R.E.: 20/60, with pinhole improvement to 20/25, and L.E.: 20/70, with pinhole improvement to 20/25. Fine keratic precipitates with a somewhat central distribution were present bilaterally. Flare and 1+ to 2+ cells were present in the anterior chambers bilaterally; cells were also present in the anterior vitreous. A pigmented chorioretinal scar did not appear active in the right peripheral fundus. Some of the peripheral retinal vessels appeared to be sheathed, particularly in the left eye. An inactive yellow scar or exudate was also present over the pars plana area inferiorly.

Results of laboratory studies showed a creatinine level of 2.4 mg/dl; urinalysis showed one to three leukocytes and zero to two erythrocytes per high-power microscopic field. Ten hyaline casts were seen on one occasion. The creatinine level subsequently decreased to 1.7 mg/dl without specific therapy. The hematocrit level was normal and the erythrocyte sedimentation rate was markedly increased. Results of a chest x-ray were normal. Serologic studies for rheumatoid factor and treponemal antibodies were negative. The immunoglobulin levels were normal. The patient was HLA-B27 negative.

Nine months after the initial examination the patient felt well except for some fatigue. He was not treated with systemic corticosteroids.

Discussion

In the five patients described herein with interstitial nephritis and uveitis, the renal disease was proven by biopsy in the three patients who received oral corticosteroid therapy and was suspected in the other two. The systemic illness always included fatigue and was frequently marked by anorexia, abdominal pain, fever, and anemia. In all patients the uveitis was anterior and eventually bilateral. In some patients increased intraocular pressure, synechiae, keratic precipitates, cells in the anterior vitreous, pars plana exudate, or intraretinal hemorrhages were also noted. In four of the five patients, the ocular disease became symptomatic months after the onset of the systemic illness. The ocular disease generally

responded well to topical corticosteroid therapy and visual acuity was maintained. Alternative diagnoses, such as systemic lupus erythematosus, syphilis, sarcoid, or Sjögren's syndrome, could not be supported by results of the laboratory studies.

Since the largest previous description of this syndrome in adults included only two patients,[5] this series represents a significant extension of previous reports. This study also includes detailed descriptions of the ocular disease in this syndrome. The patients described herein resemble those described previously in terms of the response of the renal disease to therapy; the bilateral, anterior nature of the ocular disease; the nature of the systemic complaints; and the female predominance. In many patients the disease has been thought to be triggered by an infection or ingestion of a medication such as an antibiotic. Many of the patients described herein had a history of antecedent use of a medication, but it was not possible to establish any causal relationship. In a previous case report, toxoplasmosis was thought to be causally related to the coexistence of bilateral iritis and interstitial nephritis.[10] However, this case report did not mention a chorioretinal lesion suggestive of toxoplasmosis, and the antibodies to toxoplasmosis may represent a coincidental finding. In some previous reports, granulomas have been found in bone marrow or lymph nodes.[3,8] In the five patients described here as well as those in previous studies,[3-11] a granulomatous uveitis was not noted. However, the absence of granulomatous-appearing keratic precipitates does not exclude a granulomatous disease process.[13]

Although the syndrome of uveitis and interstitial nephritis is rarely recognized, I suspect that it occurs more commonly than it is diagnosed. At the Oregon Health Sciences University uveitis clinic, it represents 2% of all patients seen to date. This is comparable to the prevalence of such diseases as iritis associated with juvenile rheumatoid arthritis, Vogt-Koyanagi-Harada syndrome, and Fuchs' heterochromic cyclitis in this referral population.[12] In Patients 4 and 5, the diagnosis was considered only retrospectively after three patients were referred with biopsy-proven interstitial nephritis. In these two patients, the systemic illness was apparent but the nature of the systemic disease was undiagnosed and the significance of the urine and renal function abnormalities was not clear. Undoubtedly this referral clinic serves a selected population, but diagnoses made in this clinic generally resemble those made in uveitis clinics under the guidance of ophthalmologists.[12] Accordingly, I recommend that all patients with a bilateral iritis in association with systemic complaints such as fatigue or fever should undergo careful evaluation of renal function.

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Quantitation of Tumor Seeding From Fine Needle Aspiration of Ocular Melanomas

Ben J. Glasgow, M.D., Harry H. Brown, M.D., Ana Maria Zargoza, M.D., and Robert Y. Foos, M.D.

Twenty-two fine needle (30 gauge) aspirations were performed in eyes enucleated for the clinical diagnosis of melanoma. Cytologic preparations were evaluated for adequacy of material, and needle tracts were evaluated for tumor implantation. A scleral marking method was used to identify all needle tracts. The number of tumor cells in tracts of direct transscleral aspirates was compared to those in tracts of indirect aspirates that traversed the anterior chamber or vitreous. Cellular material obtained with 30-gauge needles was sufficient for the diagnosis of malignant melanoma in all but one case. While 14 of 21 (67%) of all fine needle aspiration tracts and eight of 15 (53%) of indirect tracts contained tumor cells, the number of tumor cells was less than that associated with tumor growth in experimental models. Indirect aspirate tracts contained significantly fewer cells than tracts of direct aspirates ($P < .001$).

INTRAOCULAR FINE NEEDLE ASPIRATION is performed in a few institutions for limited indications.[1-3] There is hesitation to perform intraocular aspiration biopsy in some institutions because of potential complications such as tumor seeding in the needle path, with resultant local or systemic implantation of malignant cells. Recent clinical studies have not demonstrated tumor recurrence or metastases resulting from intraocular fine needle aspiration,[1-8] even though rare tumor cells have been identified in intraocular fine needle tracts.[9-11] However, these studies were not successful in identifying all of the tracts and the number of seeded cells was not quantified.

To lessen the risk of extraocular seeding, a transocular (indirect) route has been recommended so that the tumor-free tissue and fluids (sclera, conjunctiva, choroid, vitreous, and aqueous humor) cleanse the needle of adherent tumor cells.[1] We are not aware of any published experimental data to support this recommendation, and intraocular aspiration biopsies have been performed by direct scleral[4,8] and transocular approaches.[1-3,5-8]

Complications, such as intraocular hemorrhage, are stated to be reduced with 24- to 26-gauge needles compared with 22-gauge needles.[1] Thirty-gauge needles have been used only rarely,[2] and the effectiveness of obtaining diagnostic cellular material with 30-gauge needles has not been thoroughly examined.

We undertook this study to devise a reliable method for identification of fine needle tracts in enucleated eyes; to determine if diagnostic samples could be obtained with 30-gauge needles; to examine histologically 30-gauge needle tracts for melanoma cells and to quantitate seeding; and to compare direct transscleral with transocular aspiration for the number of melanoma cells seeded.

Material and Methods

Between August 1986 and October 1987, we performed 22 fine needle (30 gauge) aspirations on 11 eyes immediately after surgical enucleation for malignant melanoma. Six of these 22 aspirates, two punctures in each of three eyes, were performed by a direct transscleral route using transillumination for accurate localization of the tumor (Fig. 1). Ten aspirates were performed by a previously described indirect

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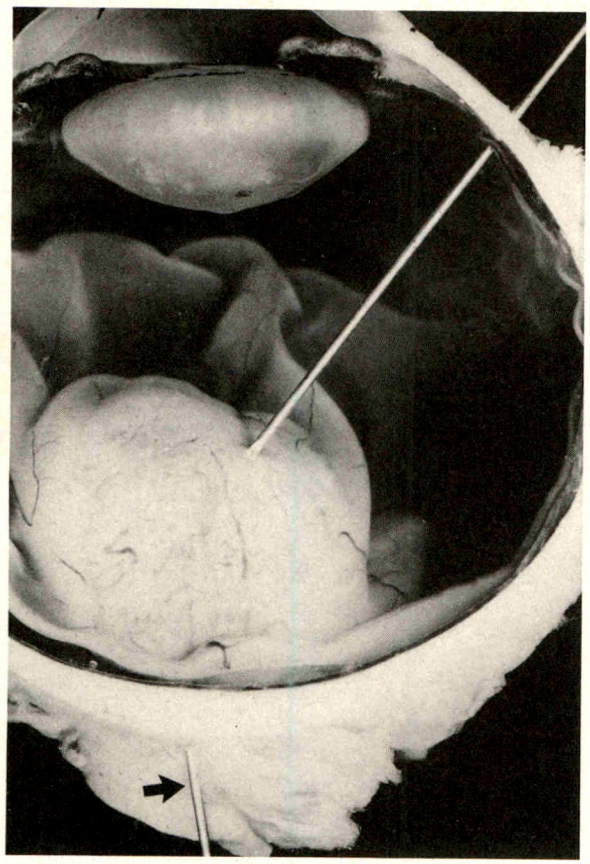


Fig. 1 (Glasgow and associates). Routes of direct (arrow) and indirect aspiration to a choroidal melanoma in a sectioned eye (×8).

transocular method using a disposable plastic syringe held in place by a metal holder and attached directly to the needle (Fig. 1).[4,8] Three of these ten aspirates were single punctures (one in each of three eyes) and seven were multiple punctures (two eyes). Six other transocular aspirates were performed by another indirect method using a needle attached to plastic tubing connected to a syringe.[2] During transocular aspirations, tumors were visualized with the aid of an operating microscope and a contact lens. The needle was inserted through the pars plana or corneoscleral limbus, visualized, and slowly advanced through the vitreous or aqueous humor into the tumor. The plunger was then retracted to apply suction, and the needle advanced slightly. Back and forth oscillatory movements of the needle were not used in indirect aspirates using plastic tubing between the needle and syringe. Suction was released before the needle was withdrawn from the tumor. The needle was then slowly removed from the eye.

In each case, aspirated material was smeared on glass slides and either rapidly air dried or fixed in 95% ethanol. Air-dried smears were fixed in methanol and prepared with the May-Grünwald-Giemsa stain. Ethanol-fixed smears were prepared with hematoxylin and eosin or Papanicolaou stains. Every smear was carefully labeled and every needle tract diagrammed so that smears could be correlated with punctures. Smears were examined immediately and the cytologic diagnoses were recorded before histologic examination.

To localize needle paths, colored ink was applied to the needle shaft before aspiration. The ink left a mark in and on the sclera during aspiration (Fig. 2). Eyes were processed using previously described methods.[12] Serial sections, 6 μm thick, were cut through each needle tract. Tracts were identified in unstained sections by finding the ink (Fig. 2, inset). All sections were stained with hematoxylin and eosin.

Nuclei of malignant cells within tracts were manually counted using an ocular grid in a ×10 eyepiece in combination with a ×40 objective lens mounted on a microscope. Criteria for identification of tumor cells included nuclear enlargement, irregular chromatin distribution, prominent nucleoli, increased nuclear to cytoplasmic ratio, and, most importantly, an appearance similar to that of the cells of the main tumor.

Statistical comparison of the number of cells

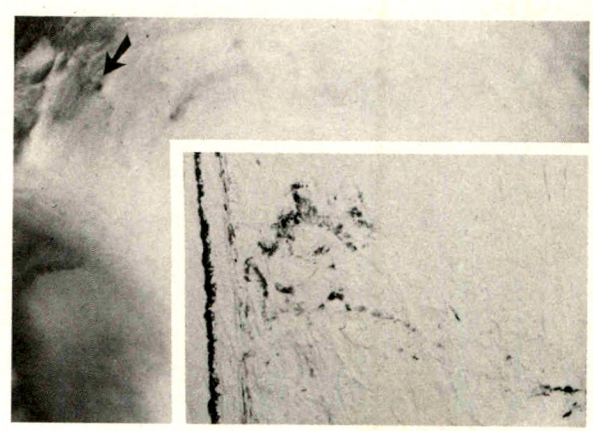


Fig. 2 (Glasgow and associates). Gross photograph shows a 30-gauge needle aspiration site that is marked by ink (arrow) (×12). Inset, Unstained histologic section demonstrates ink within the needle tract (×50).

in direct scleral and indirect needle tracts was performed using hypothesis testing to determine if the mean number of cells in the transscleral aspirates (M_X) was greater than the mean number in transocular tracts (M_Y)[13] (H_0: $M_X \leq M_Y$ and the alternate hypothesis H_a: $M_X > M_Y$). Assumptions included that the samples were independently and randomly drawn from their respective populations. The nonparametric Mann-Whitney test was used to obtain a test statistic.[13]

Results

We performed 22 needle aspirations in 11 eyes enucleated for the clinical diagnosis of malignant melanoma. Nine eyes contained choroidal melanomas; two contained ciliary body melanomas. In all but one case, 30-gauge aspirates yielded diagnostic malignant cells. In this case the tumor was a small and slightly elevated choroidal melanoma, and the aspirate showed abundant normal retinal tissue but no malignant cells. Gross examination showed that the puncture mark was about 1 mm away from the tumor. This was considered a technical error and the needle tract was not serially sectioned.

Aspirates from spindle cell melanomas showed tight clusters and single spindle cells with nuclear indentations and fine granular cytoplasmic brown pigment (Fig. 3). Epithelioid melanomas demonstrated less cohesive cell clusters; larger cells with more abundant cytoplasm; and larger, round to oval nuclei with more conspicuous nucleoli (Fig. 4). Intracellular pigment was present in every aspirate and appeared green on May-Grünwald-Giemsa-stained smears and brown on Papanicolaou- and hematoxylin and eosin-stained preparations.

All examined needle tracts were successfully outlined with ink and were identified grossly and in unstained sections by the histotechnologist (Fig. 2). Serial sections of all six direct scleral needle tracts showed sheets and numerous single malignant cells (Fig. 5). Malignant cells were found in serial sections of nine of 15 transocular (indirect) needle tracts (Fig. 6). In most indirect tracts only a few of the sections demonstrated malignant cells. Malignant cells were present in tracts of transocular aspirates done by both methods. Melanoma cells were observed in eyes punctured only once, and in first and subsequent tracts of eyes punctured multiple times. The number of malignant cells was significantly less ($P < .001$) in transocular aspirates than in transscleral aspirates (Table 1).

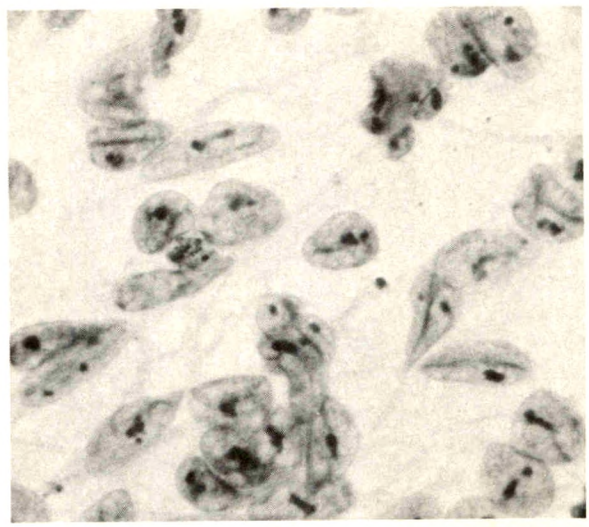


Fig. 3 (Glasgow and associates). Needle aspiration smear of a spindle cell melanoma demonstrates elongated nuclei, small nucleoli, and nuclear indentations (hematoxylin and eosin, ×788).

In five cases tumor cells were found in the

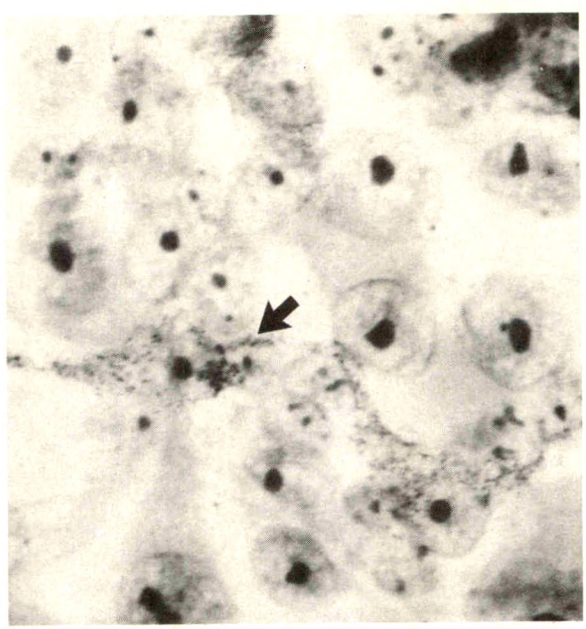


Fig. 4 (Glasgow and associates). Aspiration smear of an epithelioid melanoma shows large, round nuclei; prominent nucleoli; and abundant cytoplasm containing pigment (arrow) (hematoxylin and eosin, ×788).

TABLE 1
NUMBER OF MELANOMA CELLS SEEDED BY VARIOUS METHODS OF FINE NEEDLE ASPIRATION

CASE NO.	NO. OF CELLS
Direct method	
1	1,961
	3,162
2	2,077
	2,050
3	926
	306
Mean ± S.D.	1,747 ± 1,000
Indirect method 1*	
4	0
	0
	0
5	10
6	Missed†
7	0
	17
	28
	83
8	10
Mean ± S.D.	16 ± 18
Indirect method 2‡	
9	10
	0
10	2
	0
11	2
	0
Mean ± S.D.	2.3 ± 3.9

*Method using syringe holder attached to syringe and needle.

†Excluded from calculations because malignant cells were not obtained by aspiration. Fine needle aspiration missed tumor.

‡Method using syringe with plastic tubing intervening between syringe and needle.

episclera (Fig. 7). In two cases malignant cells were present in the vitreous or aqueous humor away from the tumor. In one case a direct needle tract transected a blood vessel in the sclera and malignant cells were present within this tract and blood vessel (Fig. 8).

Discussion

Tumor seeding leading to metastasis has been reported in nonocular tissue biopsy specimens using percutaneous Trucut,[14] Vim-Silverman,[15-17] Moonen,[18] Turkel,[19] 14-gauge,[20] and unspecified types of needles.[21] However, these techniques are not comparable to fine needle aspiration because larger gauge needles are used or core biopsy specimens are taken, or both.

Nineteen cases of metastases developing at fine needle (18 to 23 gauge) aspiration biopsy sites from the lungs, liver, prostate, kidneys, pancreas, mediastinum, and retroperitoneum have been reported (Table 2).[22-40] Often, the techniques used were similar to those used in

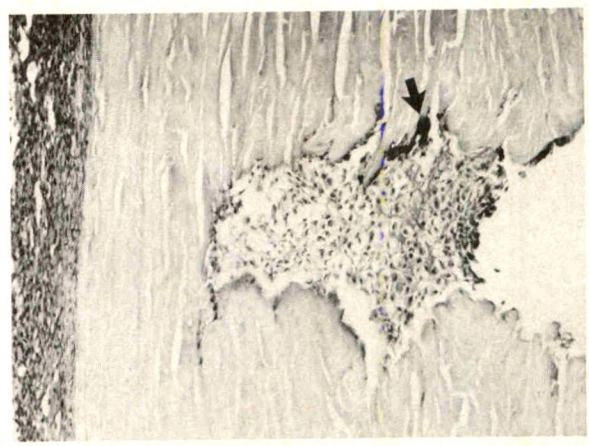


Fig. 5 (Glasgow and associates). Histologic section shows a choroidal melanoma (left) and a direct fine needle aspiration tract containing melanoma cells. Ink outlines the tract (arrow) (hematoxylin and eosin, ×125).



Fig. 6 (Glasgow and associates). Histologic section of the pars plana after indirect needle aspiration demonstrates ink lining the needle tract that contains melanoma cells (hematoxylin and eosin, ×788).

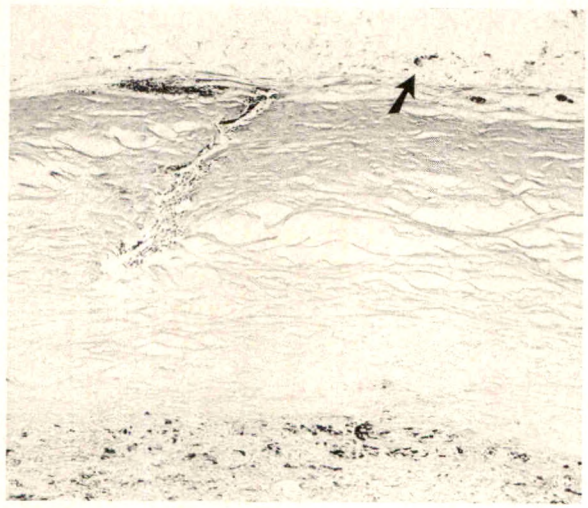


Fig. 7 (Glasgow and associates). Photomicrograph demonstrates choroidal melanoma (bottom), tumor within the direct aspiration tract, and tumor cells in the episclera (arrow) (hematoxylin and eosin, ×50).

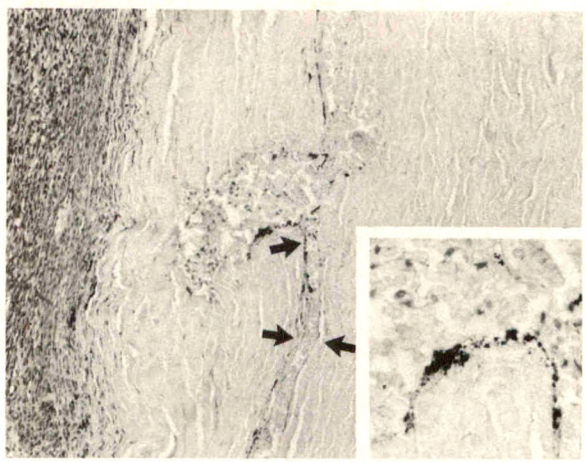


Fig. 8 (Glasgow and associates). Light micrograph shows a direct fine needle tract that traverses a scleral vein (arrows) (×125). Inset, Higher magnification demonstrates tumor cells and blood within the tract and vein (hematoxylin and eosin, ×323).

TABLE 2
CASE REPORTS OF FINE NEEDLE ASPIRATION IMPLANTATION METASTASES*

STUDY	YEAR	NEEDLE GAUGE	NO. OF PASSES	SITE	MONTHS TO METASTASIS
Sinner and Zajicek[22]	1976	18–20	NS	Lung	5
Gibbons, Bush, and Burnett[23]	1977	18	NS	Kidney	20
Ferrucci and associates[24]	1979	22	10	Pancreas	3
Smith and associates[25]	1980	NS†	NS	Pancreas	3
Woyke, Mazurk, and Frycz[26]	1982	20	1	Lung	2
Hidai and associates[27]	1983	23	NS	Liposarcoma	60
Oiwa and associates[28]	1985	NS†	NS	Mediastinum	NS
Persson[29]	1985	20	NS	Cecum	24
Burlefinger, Voeth, and Ottenjann[30]	1985	21	Several	Pancreas	6
Carabalona and associates[31]	1985	21, 23	3	Duodenum	10
Caturelli and associates[32]	1985	22	2	Pancreas	2
Moloo and associates[33]	1985	23	2	Lung	13
Pongrac and associates[34]	1985	NS†	1	Lung	12
Muller and associates[35]	1986	22	1	Lung	0.5
Frohlich, Fruhmorgen, and Seeliger[36]	1986	20, 22	3	Pancreas	2
Wehle and Grabstald[37]	1986	20	1	Kidney	48
Rashleigh-Belcher, Russell, and Lees[38]	1986	19, 22	10	Lung	6
Onodera and associates[39]	1987	22	1	Liver	3
Habscheid and Kirchner[40]	1987	NS†	NS	Pancreas	4

*NS, not specified.

†Not specified, but all needles ranged from 18 to 23 gauge.

TABLE 3
CLINICAL STUDIES OF INTRAOCULAR FINE NEEDLE ASPIRATION*

STUDY	NO. OF CASES	NEEDLE GAUGE	NO. DIAGNOSTIC†/ TOTAL	LENGTH OF FOLLOW-UP (MOS)	ASPIRATION METHOD
Jakobiec and associates[1]	6	22–26	6/6	12–36	Indirect
Augsburger and associates[3]	27	25 (22–30)‡	10/11	4.5–23	Indirect
Czerniak and associates[4]	19	22	16/19	2–24	Direct
Char and Miller[5]	1	25	1/1	NS	Indirect
Char, Ljung, and Miller[6]	59	NS	54/59	NS	Indirect
Midena and associates[7]	16	22–25	16/16	10–43	Indirect
Davey and associates[8]	6	25	3/3	8–10	Direct/indirect
Gonzáles Vanrell, Pateryro, and Grosso[50]	2	23	2/2	NS	Direct

*NS, not specified.
†Includes only cases in which cytologic diagnosis was confirmed by histologic examination.
‡(), range of needle gauges used.

transocular aspiration biopsies in that needles traversed cavities and tumor-free tissue (skin, muscle, peritoneum, and the like) to reach the neoplasms. In two cases, histologic sections showed tumor cells centered in the scar of the old needle tract.[23,35] In other cases, tumor cells were assumed to originate from the site of the aspirate, but skin metastases could not be excluded. Even if these 19 cases are considered valid, the incidence of tumor implantation from fine needle aspiration is low. One survey estimated that seeding with resultant metastases occurred clinically in only one case in 20,000.[41] In studies reporting both cases of needle tract implantation and the total number of aspirates performed, the incidence of metastases caused by fine needle aspiration was only one in 1,264,[22] one in 1,674,[34] one in 31,[27] and one in 15.[28] These, like most, studies dealing with fine needle aspiration are retrospective and details of clinical follow-up examinations are usually not reported. Therefore, the incidence of seeding may have been underestimated. Of 6,500 fine needle biopsies performed at our institution from 1983 to 1987, no cases of tumor implantation metastases have been documented. However, many of these patients have not been carefully followed up. In any case, tumor implantation with metastases has not been reported with needles that are 25 gauge or smaller.

Intraocular needle biopsies have been performed since 1895.[42] Orbital metastases[43] and tract seeding[44,45] of malignant melanomas have been reported from intraocular needle biopsy, but because details of the biopsy technique and needle gauge were not specified, these and other cases[46-48] are not comparable to current studies using intraocular fine needle aspiration. Similarly, cases in which sclera was incised[49] are difficult to compare to cases performed today, which do not involve scleral incision.

At least 132 cases of intraocular fine needle biopsy have been reported in which the aspiration technique and needle gauge were described (Table 3). Even in patients in whom enucleations were not done after fine needle aspiration, tumor growth has not yet been demonstrated at the aspiration site.[3,10] In some instances clinical follow-up exceeds two years, yet no tumor implantation has been reported. These cases do not include those described by Rodriguez[9] in which vitreous and aqueous humor were aspirated with 19-gauge Scheie needles and seeding of retinoblastoma cells was discovered in two eyes at three and six weeks after aspiration. However, retinoblastomas may be more susceptible to seeding than ocular melanomas and aspiration biopsy of this neoplasm is not presently recommended.[10,11]

Karcioglu, Gordon, and Karcioglu[11] identified tumor cells in six of 11 tracts from transocular fine needle aspiration performed on enucleated eyes. Augsburger[10] proposed that this incidence was higher than that observed clinically and that differences in technique might be responsible. Because multiple punc-

tures had been performed in these experimental studies,[11] it was suggested that seeding occurred in the second, third, or fourth puncture related to loss of vitreous and decreased intraocular pressure produced by the first puncture.[10] Our study does not support this hypothesis because each transocular aspirate was labeled and tracts of first aspirates contained melanoma cells as frequently as did second, third, and fourth aspirates. Furthermore, two of three eyes in which only one puncture was performed contained melanoma cells in the tract. Tumor seeding occurred with both variations of transocular techniques, that using plastic tubing between the syringe and needle[2] and that with the syringe attached directly to the needle.[8] No statistically significant difference was noted in the mean number of cells seeded by either technique. However, only a few cells were present in the tracts of transocular aspirates. These could be easily missed without effectively marking and serially sectioning the tract. The yield of 53% (eight of 15) tumor-positive indirect tracts in our study reflects complete sectioning of entire tracts. While this percentage appears high, experimental studies demonstrated tumor within lung fine needle aspiration tracts in 89% of cases,[51] yet only a few clinical cases of seeding have been demonstrated.[23,26,34,35,48]

Tumor autotransplantation studies indicate approximately 0.8 to 1 $\times$ 10^6 cancer cells in humans are needed to allow successful implantation.[52,53] Radioactive labeling studies of ascites tumors in mice indicate that 10^3 to 10^4 tumor cells are seeded from fine needle aspiration biopsy of solid tumors.[54] Similarly, we counted up to 3,162 melanoma cells in direct fine needle tracts and fewer in indirect tracts. Therefore, the number of tumor cells seeded appears less than that required for successful implantation of aggressive tumors under experimental conditions. These data could explain the disparity between clinically observed absence of tumor growth at intraocular fine needle aspiration sites[10] and the high frequency of seeding demonstrated in experimental studies.[11] Perhaps there are too few seeded tumor cells to implant successfully or ocular melanomas are less aggressive than malignant cells used in the autotransplantation studies, or both.[51,52]

In this study, transocular aspirates resulted in significantly fewer tumor cells within tracts than direct aspirates and three orders of magnitude fewer than necessary for survival of tumor implants. These data support the theory that transocular aspirates would be less likely to result in extraocular seeding than direct aspirates.[1] Possible explanations include less seeding because fewer cells are obtained with indirect aspirates or that tumor cells are removed from the needle by intervening tissue. Vitreous seeding could occur in transocular aspirates, but experimental animal studies have demonstrated that tumor cells are difficult to transplant in the vitreous.[55] Additionally, since most human eyes are enucleated immediately after a positive fine needle biopsy, tumor cells seeded in the vitreous are removed. The degree and significance of vitreous and aqueous humor seeding were not addressed in this study.

Implantation of cells within the sclera may result from several mechanisms. The cells may be pulled from the needle or tumor interior by the vacuum created by needle removal from the scleral tract, even though the plunger has been released and pressure has been allowed to equilibrate. This would account for the sheets of cells that are directly contiguous with the tumor observed in direct aspirates and fewer cells in indirect tracts. Alternatively, cells may adhere to the outside of the needle and be left when the needle is withdrawn.

Theoretically, cells seeded in the scleral or choroidal vasculature could spread to distant organs by vascular routes. In one of our cases, the vasculature appeared to be seeded but by fewer cells than required to cause experimental metastases by intravenous injection of melanoma cells in mice.[56]

In this study, 30-gauge needles were chosen on the premise that their small diameter might result in fewer complications than large bores and, therefore, be preferable if adequate material could be obtained. Intraocular hemorrhage is stated to be less with 24- to 26-gauge needles than with 22-gauge needles.[1] At least one diagnostic intraocular fine needle aspiration biopsy has been performed with a 30-gauge needle.[3] In our study, 30-gauge needles were adequate for obtaining diagnostic cytologic material, but, in general, the tumors were larger and perhaps easier targets than in clinical cases performed for diagnostic uncertainty. Therefore, 30-gauge needles will have to be shown to provide adequate material consistently in a clinical setting before their routine use can be recommended.

The presence of tumor cells in fine needle tracts may have more significance in nonocular tissues where direct aspirates are performed routinely with much larger bore needles on tumors more anaplastic than ocular melano-

mas. This might account for the cases of tumor implantation after fine needle aspiration of nonocular tissues. Considering the differences in techniques and the few cells implanted, one would expect indirect ocular fine needle aspiration biopsy with 30-gauge needles to be less likely to produce significant tumor implantation than nonocular aspiration with 18- to 23-gauge needles.

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OPHTHALMIC MINIATURE

He had always one eye wide open, and one eye nearly shut; and the one eye nearly shut was always the expressive eye.

F. G. de Fontaine, *The Fireside Dickens*
New York, Dillingham, 1888

Maternal Orbital Hematoma Associated With Labor

Daniel M. Jacobson, M.D., Kamel Itani, M.D., Kathleen B. Digre, M.D., Karl C. Ossoinig, M.D., and Michael W. Varner, M.D.

We examined two women with orbital hematomas that occurred during labor. Both women developed sudden diplopia, proptosis, and orbital pain. The location of the hematoma was confirmed by orbital echography and computed tomography. The patients were observed without surgical intervention. Neither patient developed clinical or echographic signs of compressive optic neuropathy. Clinical resolution occurred during the following two weeks. Serial standardized orbital echographic examinations documented resolution of the hematomas.

MOST ORBITAL HEMATOMAS are caused by trauma. Spontaneous hematomas in the orbit that are not associated with trauma, vascular anomalies, or tumors are rare. In previous reports of so-called spontaneous orbital hematomas there was a history of remote trauma,[1,2] and occurrence during coughing and vomiting[1] or physical exertion.[3] The latter two associations suggest that the pathogenesis was somehow related to the increased orbital venous pressure that resulted from straining.

The peripartum is a period of increased risk for certain cerebrovascular events, such as aneurysmal expansion and rupture,[4] development of carotid-cavernous sinus fistulae,[5] and cortical vein and sinus thrombosis.[6] Because these disorders can impair ocular motility, ophthalmologists and neurologists may be asked to examine such patients early in the course of illness. Prompt identification of the responsible lesion is critical since some disorders, aneurysmal expansion and compressive optic neuropathy for example, may require urgent intervention.

We examined two patients with sudden ophthalmoplegia that occurred during labor and was caused by orbital hematomas. Although this association is rare, orbital hematoma should be considered in the differential diagnosis of ophthalmoplegia occurring during labor or in the immediate postpartum period.

Case Reports

Case 1

A 28-year-old primigravida woman had an uncomplicated antepartum course and presented in labor at full term. A 90-minute second stage of labor and maternal fatigue prompted a low forceps delivery. As her healthy 4,230-g newborn was handed to her, she experienced vertical diplopia. The obstetric staff noted right-sided blepharoptosis. The diplopia persisted and was exacerbated by looking up or to the left. Twelve hours after delivery the patient noted a dull right retro-orbital pain, which increased during movement of the eye. Her medical history was unremarkable.

On examination, visual acuity was 20/15 in each eye. Color vision, as screened with pseudoisochromatic plates, was normal. Visual fields were full to confrontation. Pupil sizes were normal in light and darkness, and both pupils reacted briskly to light stimulation; there was no relative afferent pupillary defect. Results of slit-lamp and ophthalmoscopic examinations were also normal. Two millimeters of axial orbital proptosis was measured in the right eye relative to the left. The globe was not displaced otherwise. There was 3 mm of blepharoptosis of the right eyelid relative to the left. The patient preferred to tilt her head to the left when looking straight forward. There was mild

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limitation to adduction and supraduction of the right eye. The blepharoptosis did not increase during sustained upward gaze or resolve after intravenous administration of edrophonium (Tensilon test).

Results of computed tomography through the posterior fossa after contrast administration were normal. Axial computed tomography of the orbits showed an extraconal mass of high density in the superior medial aspect of the right orbit (Fig. 1). Results of laboratory studies were normal for bleeding time, prothrombin time, activated partial thromboplastin time, and platelet count.

Standardized echography showed an extensive, firm, superonasal extraconal hematoma that extended from the anterior orbit into the midorbit between the 11 and 4 o'clock meridians (Figs. 2 and 3, top). The hematoma was situated between the periorbita and the levator muscle and involved the trochlea and the superior oblique muscle. The hematoma was 7.1 mm thick in the 1:30 meridian (Fig. 3, top). No morphologic signs of optic nerve compression by the hematoma, such as increased subarachnoidal fluid surrounding the anterior portion of the orbital optic nerve, were detected echographically.

On discharge two days later, results of the examination remained unchanged. Her pain and diplopia gradually resolved over the following week. Two weeks after the onset of ocular symptoms her ductions were full and the blepharoptosis had resolved.

An echographic follow-up examination on day 7 showed a marked decrease in the size of the hematoma, which now extended between the 12 o'clock and 2:30 meridians only and had become slightly compressible. Further echographic examinations performed three and four weeks after onset demonstrated continued decrease in the size of the hematoma to 2.8 mm (Fig. 3, middle). A repeat computed tomographic scan of the orbits, before and after contrast administration, showed resolution of the original lesion and no other abnormality. A final echographic evaluation seven weeks after onset showed complete resolution of the hema-

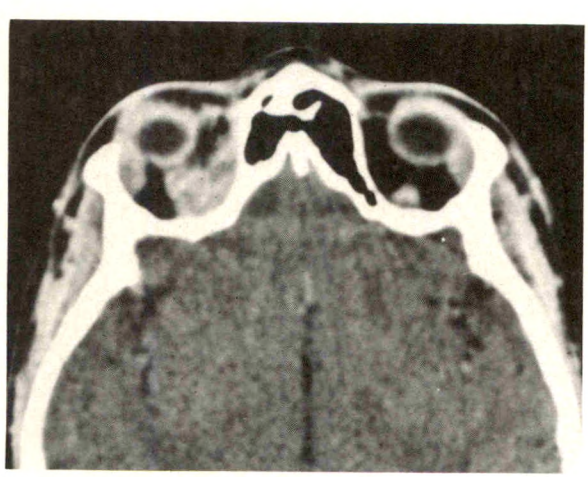


Fig. 1 (Jacobson and associates). Patient 1. Computed tomography shows high-density, extraconal mass in the superior-medial aspect of the right orbit.

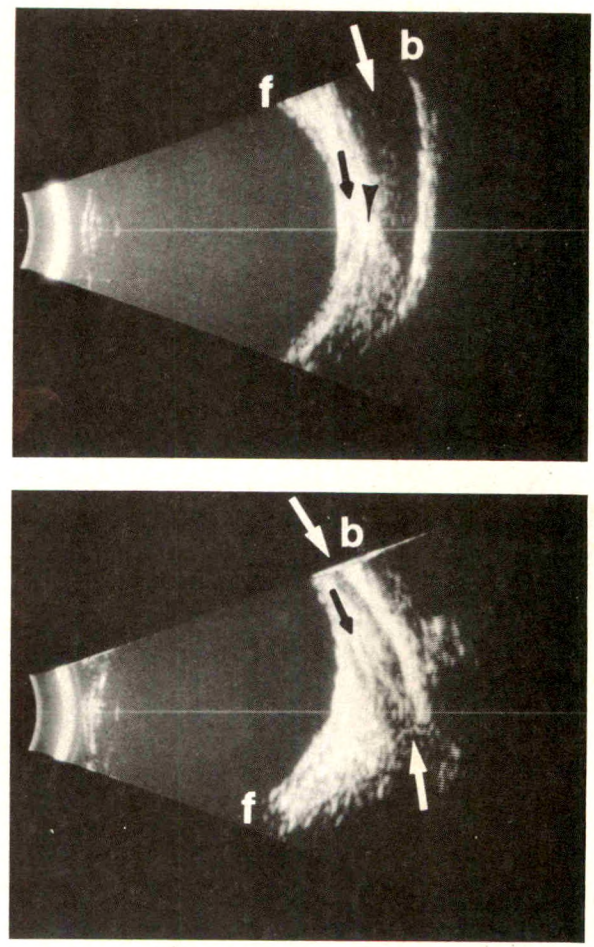
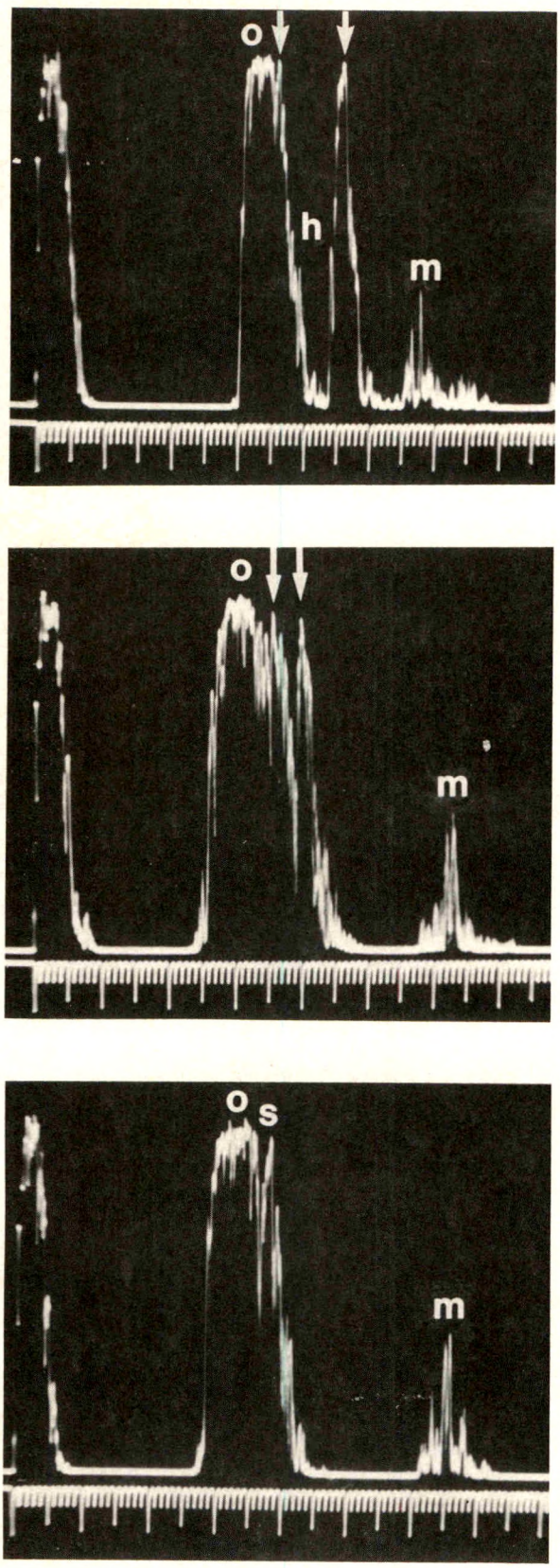


Fig. 2 (Jacobson and associates). Patient 1. B-scan echography representing a transverse cut through the anterior superior orbit across the 12 o'clock meridian (top) and a longitudinal section from the anterior to mid-orbit along the 1 o'clock meridian (bottom). f, fundus; white arrows, hematoma between orbital roof and levator muscle (see also Fig. 4, bottom); black arrows, inserting tendon of superior rectus muscle; black arrowheads, levator muscle; b, bony roof.



toma and a normally thick and reflective right superior oblique muscle in the area of the previous hematoma (Fig. 3, bottom). The patient has had no further symptoms after 18 months of follow-up.

Case 2

A 20-year-old primigravida woman had an uncomplicated antepartum course and presented in labor at full term. Five minutes into the second stage of labor she felt a "pop" in her left eye while she performed a Valsalva's maneuver during a contraction. She then noted blurred vision in that eye. The attending nurse recognized that her left eye was "swollen." After delivery the patient felt a dull pressure above her left eye and noted vertical diplopia, particularly on upward gaze. Her medical history was unremarkable.

On examination, visual acuity was R.E.: 20/15 and L.E.: 20/25. Visual fields were full to confrontation. The pupils were equal in size and both pupils reacted briskly to light stimulation; there was no relative afferent pupillary defect. Results of slit-lamp and ophthalmoscopic examinations were normal. Two millimeters of axial orbital proptosis was measured in the left eye relative to the right. The globe was not displaced otherwise. There was 3 mm of blepharoptosis of the left upper eyelid relative to the right. There was a mild deficit in supraduction of the left eye, but all other ductional movements were full.

Standardized echography was performed to rule out a varix or arteriovenous malformation, but it demonstrated an extensive subperiosteal hematoma instead. A hard, sharply delineated, low-reflective, extraconal mass lesion was detected in the superior left orbit above the levator muscle, extending from the anterior orbital

Fig. 3 (Jacobson and associates). Patient 1. A-scan echography from the anterior orbit at the 1:30 meridian obtained during initial examination (top), at three weeks (center), and at seven weeks (bottom). h, hematoma (extremely low reflective); arrows, inferior (left) and superior (right, periorbita and bone spikes) surface of the hematoma; m, multiple signals (artifact); o, soft orbital tissues in superonasal anterior orbit; s, superior oblique muscle (cross section behind the trochlea). Note the marked decrease in thickness of the hematoma (between arrows) seen during the follow-up examination three weeks after onset (center) as compared to the initial examination (top).

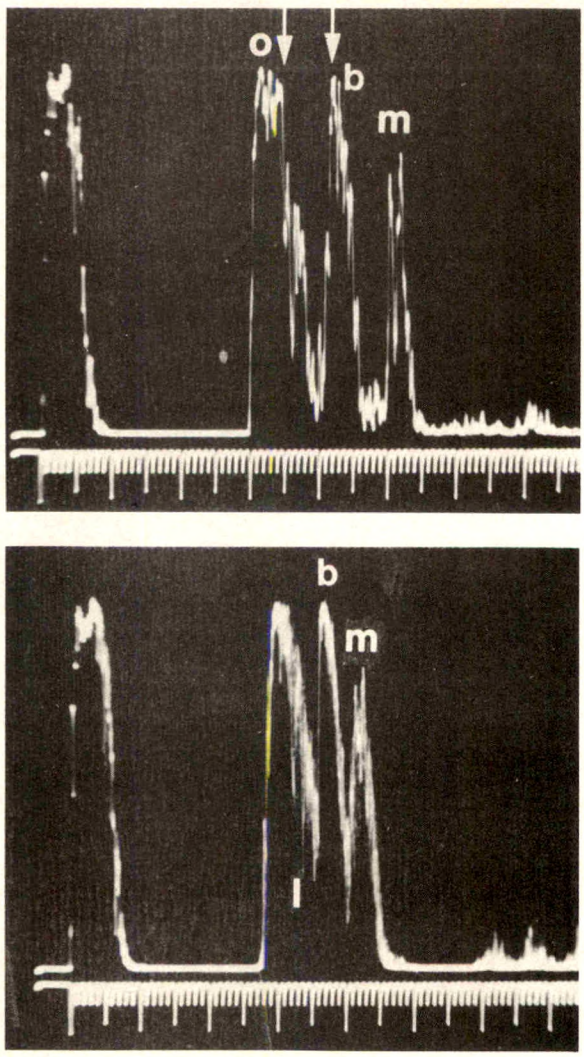


Fig. 4 (Jacobson and associates). Patient 2. A-scan echography shows a subperiosteal hematoma in the left superior orbit. The maximum thickness of the hematoma measured 6.2 mm (between arrows in top echogram). The location of the hematoma above the levator muscle is obvious from the bottom echogram: the blurred spikes on the left of the hematoma pattern represent the levator muscle (the blurring is caused by blinking). Arrows, inferior (left arrow) and superior (right arrow) surfaces of the hematoma at its maximum width in the anterior 12 o'clock meridian; b, bone spikes; l, levator muscle; m, multiple spikes (artifact); o, soft orbital tissues. Note the sharp rise and fall of the right and left surface spikes as indicated by the right and left arrows in the top echogram (smooth surfaces of bone and periorbita).

rim to the orbital apex between the 9:45 and 1:45 meridian bony suture lines (Figs. 4 and 5, top). The hematoma was 6.2 mm thick in the midorbit at the 12 o'clock meridian. No echographic signs of compressive optic neuropathy were detected.

Axial computed tomography of the orbits showed an extraconal mass of high density in the most superior aspect of the left orbit (Fig. 6). Results of laboratory studies were normal for prothrombin time, activated partial thromboplastin time, and platelet count.

The patient returned 11 days later and reported that the pressure sensation and diplopia had gradually resolved. Visual acuity was 20/20 in each eye, and there was no relative afferent pupillary defect. She had minimal limitation of supraduction of the left eye and less blepharoptosis than previously noted. Her proptosis had resolved. Repeat standardized echography demonstrated that the subperiosteal hematoma had decreased markedly and now had a maximum thickness of 2.5 mm (Fig. 5, bottom).

The patient failed to return for further examination, but when contacted by telephone two years later, reported no further blurry vision, diplopia, pain, proptosis, or blepharoptosis.

Discussion

Three cases of maternal orbital hematoma associated with labor and the postpartum period have been previously reported. Birch-Hirschfeld[7] cited two cases in his extensive review of 80 reports of orbital hematomas collected from the literature before 1930: one patient (described by Gayet in 1898) was a 35-year-old woman who suffered an orbital hemorrhage 15 days after her tenth delivery; the second case (described by Böhm in 1899) concerned a woman with exophthalmos six to seven hours after delivery. In a series of 17 patients with "spontaneous" orbital hematomas reported in 1979, Krohel and Wright[8] included a 28-year-old woman who developed a hematoma 24 hours after labor. Few clinical details were provided in these reports.

The hemodynamic events that occur during labor may have precipitated the orbital hematomas in our two patients. During the second stage of labor, straining against a closed (or partially closed) glottis rapidly increases intra-abdominal and intrathoracic pressures (Valsalva's maneuver). These greatly augmented pressures can be directly transmitted through the jugular veins to the orbital veins since the latter do not contain valves.[9] Uterine contraction also results in a 500-ml increase in

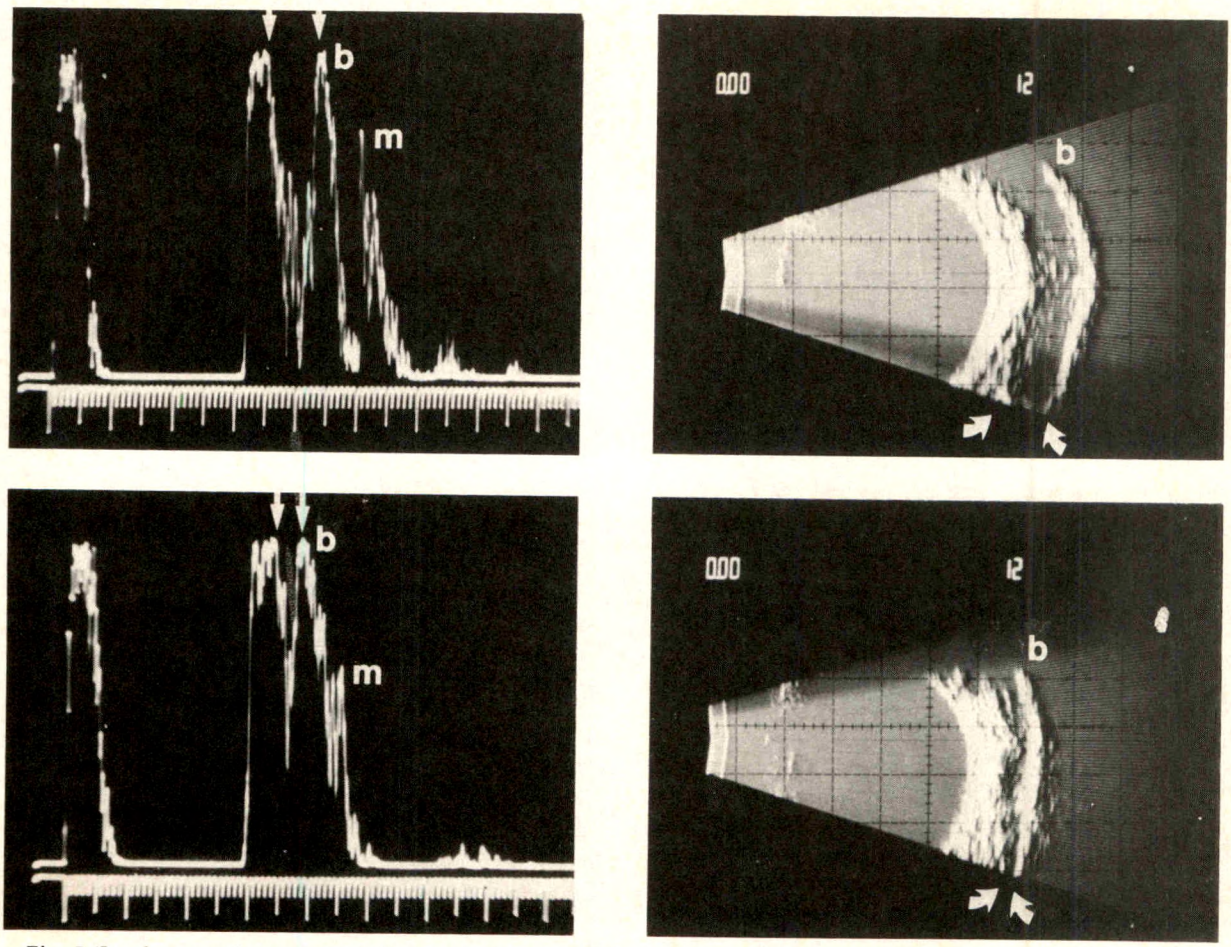


Fig. 5 (Jacobson and associates). Patient 2. A-scan (left) and B-scan (right) echograms displaying the maximum width (6.2 mm) of the left superior subperiosteal hematoma at the 12 o'clock meridian during the initial examination (6.2 mm, top echograms) and 11 days later (2.5 mm, bottom echograms). Arrows, inferior (left signals) and superior (right signals) borders of the hematoma; b, signals of bony roof; m, multiple spikes (artifact). Note the sharp drop (left arrows) and sharp rise (right arrows) of the surface spikes in the A-scan echograms, indicating the smooth surfaces of the detached periorbita (left surface spike) and of the bare bone (right surface spike).

circulating maternal blood volume.[10] Uterine contraction alone can cause a 40- to 50-mm Hg rise in right atrial pressure,[10] which is also directly transmitted to the orbital veins.

Other cases of orbital hematomas have occurred during other strenuous situations, such as coughing[1,7] and physical exertion.[3] Since the orbital location of the hematoma in our two patients was extraconal and superior, a probable source of hemorrhage was from one of the branches of the superior ophthalmic vein. These small tributary veins are markedly tortuous and consist of many plexiform anastomoses.[9] A preexisting area of focal weakening may have ruptured from the enhanced luminal pressures generated during the second stage of labor.

When examining a patient with ophthalmoplegia that occurs abruptly during labor or in the immediate postpartum period, the full spectrum of diagnostic possibilities must be considered, since urgent intervention may be required in some cases. Proptosis, globe displacement, restrictive ophthalmoplegia, and localized pain suggest that the process is orbital in location. Orbital lesions to consider include idiopathic hemorrhage, hemorrhage from vascular anomalies (for example, varices, arteriovenous shunts), or tumors (for example, lymphangioma).

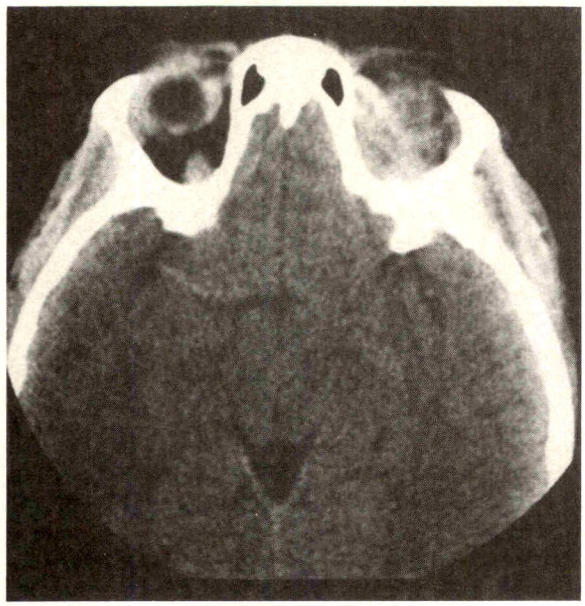


Fig. 6 (Jacobson and associates). Patient 2. Computed tomography shows a poorly defined, high-density, extraconal mass in the superior aspect of the left orbit.

Cavernous sinus involvement from an expanding carotid artery aneurysm, carotid-cavernous fistula, or thrombosis should be suspected if some combination of cranial nerves III, IV, VI, or V_1 are involved with, or without, a subjective or objective bruit. If a pupil-involving third nerve palsy is identified, an aneurysm either at the junction of the internal carotid artery and posterior communicating artery or, less often, at the basilar artery tip needs to be urgently excluded.

Intraparenchymal cerebral hemorrhage from toxemia or a ruptured aneurysm can produce a third or sixth cranial nerve palsy from increased intracranial pressure or tentorial herniation, or from direct brainstem insult. Obviously, the ophthalmoplegia will not be the only finding in these neurologically ill patients. Likewise, superior sagittal sinus thrombosis usually produces ophthalmoplegia from increased intracranial pressure. These patients have severe headache, seizures, focal neurologic deficits, and a decreased level of consciousness.

Drug toxicity, particularly one of magnesium sulfate or narcotic analgesics, may cause diplopia by impairing accommodation and vergence mechanisms. Finally, myasthenia gravis may become manifest during the puerperium.[11]

Standardized echography is a highly sensitive and specific test for detecting and differentiating orbital lesions.[12-16] Orbital echography identifies and classifies orbital hematomas and readily detects underlying lesions, such as arteriovenous malformations, varices, and lymphangiomas. Standardized echography is crucial for the early detection of optic nerve compression,[17] the most dangerous complication of orbital hematomas,[18,19] or for morphologic proof of such optic neuropathy when functional loss occurs. Echography is also the safest and most accurate follow-up procedure in managing this condition.

Additional high-resolution computed tomography of the brain, including axial and coronal cuts through the orbits and parasellar regions, is important to detect intracranial aneurysms, subarachnoidal hemorrhages, intraparenchymal hemorrhages, and lesions in the cavernous sinus. If standardized echography is not available or does not show an orbital cause of the signs and symptoms, such a computed tomographic scan examination should be urgently performed in patients with intrapartum or postpartum ophthalmoplegia. If the echographic or computed tomographic scan examination fails to define the responsible abnormality, or if the ophthalmoplegia is associated with pupillary involvement, then cerebral arterial angiography is indicated to exclude the presence of an intracranial aneurysm.

If the initial examination identifies an orbital hematoma, the patient requires frequent clinical and echographic examinations, with particular attention paid to the morphologic and functional signs of optic nerve compression. The benign outcome in our two patients suggests that conservative observation is an acceptable option of management, provided that optic nerve function remains normal and repeat echography indicates a decrease in the size of the hematoma. If evidence of compressive optic neuropathy exists initially, or develops during the follow-up period, high doses of systemic corticosteroids or surgical evacuation may be indicated and can restore vision to normal if performed early enough.[8,18,19]

Standardized echography offers clear advantages over computed tomography in observing these patients. It is fast, specific, and harmless, which makes it ideal for frequent follow-up examinations. It aids in diagnosing compressive optic neuropathy. It defines the location of the hematoma and accurately measures its size. Finally, it can be performed in the operating

room for exact localization and instant confirmation of complete drainage if surgical evacuation of the hematoma is performed.

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OPHTHALMIC MINIATURE

In a space no longer than it takes to open one's eyes she was back in her accustomed life, in a leap was transferred to daylight from darkness. And yet, as by the mere closing of eyelids, one can surmise a darkness stranger than any star has pierced, a darkness of no light which only the blind can truly possess, she knew that by a moment's flick of the mind she could levant into a personal darkness, an unknown aspect of Sophia as truly hers as one may call the mysterious sheltering darkness of one's eyelid one's own.

Sylvia Townsend Warner, *Summer Will Show*
New York, Viking Penguin Inc., 1936, p. 36.

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EDITORIAL

Ophthalmic Miniatures

Frank W. Newell

Beginning with the January 1988 issue, the ophthalmic miniatures have reappeared in THE JOURNAL after an absence of six years. In 1982 production problems necessitated that we discontinue the use of these contributions from readers from all over the world. The late Derrick Vail originated these little pieces in 1948, at which time they were called historical miniatures. In 1950 the name was changed to ophthalmic miniatures.

In the past, ophthalmic miniatures have consisted of a potpourri of material relating to the eyes. The material has consisted of couplets from Ogden Nash to Shakespeare's sonnets, pictures of ophthalmic instruments from old catalogs, and snippets of writers ranging from Aeschylus to Saul Bellow.

THE JOURNAL is exceptionally dependent upon readers to submit these little nuggets from their extravocational reading. We always acknowledge receipt of the material in THE JOURNAL office, but do not publish the names of those who submit the miniatures. The main reason for this is economy of bookkeeping, but some readers are reluctant to reveal their eclectic reading tastes. All of us in the editorial office enjoy this section. We hope our readers once again submit material for the ophthalmic miniatures. Please provide the full name of the author, the source of the miniature, the publisher and publication date, as well as the page number. If possible also please send a photocopy of the original source.

LETTERS TO THE JOURNAL

Intraocular *Staphylococcus aureus* Abscess Masquerading as Chronic Uveitis

Richard H. Manka, M.D., Robert A. Nozik, M.D., and Walter H. Stern, M.D.

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An 86-year-old man underwent a right extracapsular cataract extraction with posterior chamber intraocular lens implantation in May 1986. A loose suture was removed in the first postoperative month. After the first month, the patient developed redness in the right eye, and reported a decrease in vision. Mild anterior chamber cellular reaction and flare were present. The patient improved on a regimen of topical and subconjunctival corticosteroids but continued to require corticosteroids over the next two months in order to suppress the low-grade inflammation.

Because of continued inflammation, he was referred to the Proctor Foundation Uveitis Clinic in October 1986. Visual acuity was 20/400 in the right eye. On examination, diffuse conjunctival injection, fine inferior keratic precipitates, and iris vessel dilation were noted. The intraocular lens was in good position with no residual cortical material visible. There was no evidence of a filtering bleb. Gonioscopy disclosed both a small hypopyon and a white lesion in the superonasal anterior chamber angle that was approximately 2 mm in diameter (Fig. 1). This lesion was not visible on routine slit-lamp examination. Results of anterior chamber paracentesis showed polymorphonuclear leukocytes, but no organisms or macrophages were seen. Aerobic and anaerobic cultures of the aqueous aspirate were negative.

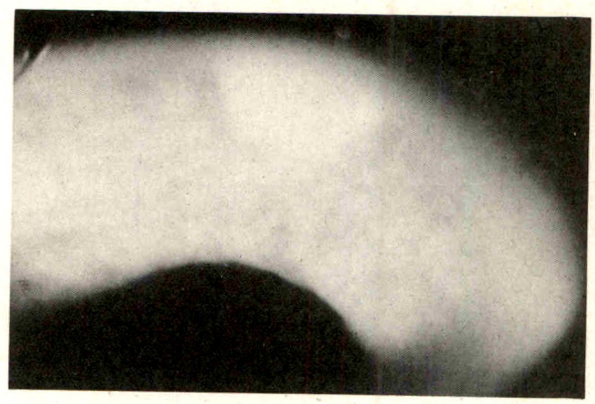


Fig. 1 (Manka, Nozik, and Stern). A white mass in the anterior chamber angle on gonioscopy.

The white lesion in the anterior chamber angle was aspirated for examination and culture with a blunt needle and a vitrectomy suction cutter. The white material was extremely tenacious and adhered to both the underlying iris and the angle structures. Although most of the white material was removed, residual material was left attached to underlying structures. Abundant *Staphylococcus aureus* grew out of the aspirate. The patient was treated with topical,

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THE JOURNAL welcomes letters that describe unusual clinical or pathologic findings, experimental results, and new instruments or techniques. The title and the names of all authors appear in the Table of Contents and are retrievable through the Index Medicus and other standard indexing services. Letters must not duplicate data previously published or submitted for publication. Each letter must be accompanied by a signed disclosure statement and copyright transfer agreement published in each issue of THE JOURNAL.

Letters must be typewritten, double-spaced, on 8 1/2 x 11-inch bond paper with 1 1/2-inch margins on all four sides. (See Instructions to Authors.) They should not exceed 500 words of text. A maximum of two black-and-white figures may be used; they should be cropped to a width of 3 inches (one column). Color figures cannot be used. References should be limited to five.

Letters may be referred to outside editorial referees for evaluation or may be reviewed by members of the Editorial Board. All letters are published promptly after acceptance. Authors do not receive galley proofs but if the editorial changes are extensive, the corrected typescript is submitted to them for approval.

These instructions markedly limit the opportunity for an extended discussion or review. Therefore, THE JOURNAL does not publish correspondence concerning previously published letters.

subconjunctival, intraocular, and systemic cefazolin sodium. The inflammation resolved over six days, visual acuity improved to 20/30 in the right eye, and the residual white material in the anterior chamber angle gradually disappeared (Fig. 2).

Intraocular *S. aureus* typically results in a fulminant, rapidly destructive endophthalmitis. In a review of 30 cases of postoperative endophthalmitis, Weber and associates[1] isolated *S. aureus* from seven cases and found that all of these cases occurred within nine days of surgery. Confino and Brown[2] reported *S. aureus* in one of three cases of postkeratoplasty bacterial endophthalmitis associated with an intrastromal suture abscess. Their patient had an acutely painful, markedly injected eye with a retrocorneal fibrin plaque, a 2-mm hypopyon, a hazy fundus reflex, and scattered vitreous opacities. Gelender[3] reported a case of *S. aureus* endophthalmitis after cataract surgery, four days after sutures had been cut. The patient experienced markedly decreased vision, intraocular inflammation, and a hypopyon. In our patient, chronic infection by a typically virulent organism may be explained by sequestration of the organism within an enclosed area. This is evidenced by the lack of growth of the initial paracentesis culture. It appears that the white lesion was an intraocular abscess in the area of the previous suture removal.

It is sometimes difficult to differentiate between sterile and infectious causes of postoperative intraocular inflammation. Recent reports of chronic *Propionibacterium acnes* and *S. epidermidis* endophthalmitis after cataract extraction have emphasized the importance of considering infectious causes of persistent postoperative intraocular inflammation.[4,5] As in other reported cases of bacterial and fungal endophthalmitis, in this case it was not necessary to remove the intraocular lens to cure the intraocular infection.

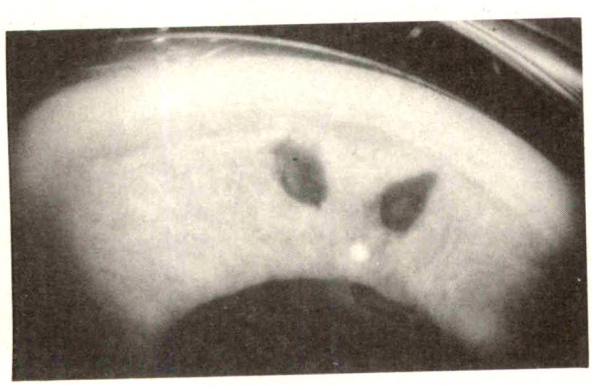


Fig. 2 (Manka, Nozik, and Stern). Postoperative appearance of the anterior chamber angle, with iridectomies resulting from adherence of the abscess to the iris.

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Chronic Herpes Zoster Virus Keratitis Associated With the Acquired Immunodeficiency Syndrome

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Herpes zoster infections can cause profound morbidity and may have important prognostic implications in persons infected with human immunodeficiency virus. In contrast to previously reported cases of herpes zoster ophthalmicus, which were characterized by severe skin

and ocular diseases, our patient had an isolated keratitis as the only persistent manifestation of herpes zoster infection.

A 32-year-old homosexual man with AIDS and severe perianal herpes simplex lesions developed vesicles on his left eyebrow, nose, and upper lip, and a left dendriform keratitis. A presumptive diagnosis of disseminated herpes simplex infection was made and he was treated with intravenous acyclovir and topical trifluridine. Although the skin lesions resolved, leaving only one scar above the eyebrow, the ocular irritation persisted.

Six weeks later, visual acuity was L.E.: 20/30. Corneal sensation was intact. On examination, three opaque dendriform lesions with accumulations of epithelial debris, irregular fluorescein staining, and underlying anterior stromal haze were noted in the superonasal quadrant of the left cornea. Despite five additional weeks of topical trifluridine and oral acyclovir therapy (200 mg, five times daily), the lesions enlarged and extended inferiorly, and the corneal sensation was lost (Figure). Visual acuity decreased to L.E.: 20/80. After medications were stopped, herpes zoster virus, not herpes simplex virus, was identified in corneal scrapings by immunofluorescence techniques and culture. A central 2.5 × 5-mm geographic epithelial defect developed. Treatment was begun with acyclovir ointment, five times daily. The epithelial defect closed within five days, but diffuse punctate keratopathy persisted. Irritation and foreign body sensation developed after eight weeks of therapy, and acyclovir ointment was discontinued. Two weeks later discomfort resolved, punctate keratopathy decreased, and visual acuity improved to L.E.: 20/70. There were no further dendriform lesions.

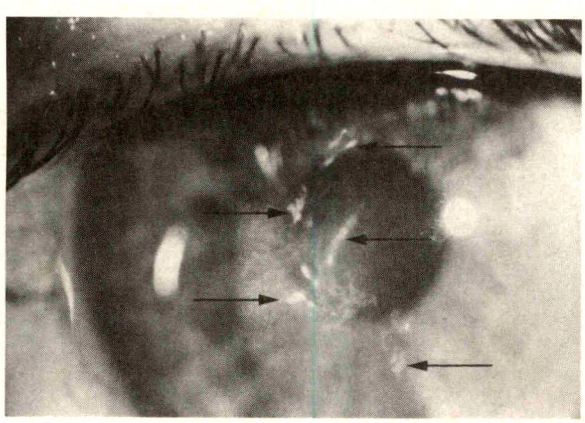


Figure (Engstrom and Holland). Chronic dendriform lesions of the cornea (arrows) caused by active herpes zoster infection in a patient with AIDS.

In previous reports, zoster ophthalmicus associated with human immunodeficiency virus infection has been characterized by severe and prolonged cutaneous lesions, keratitis, and anterior uveitis.[1] In the absence of these typical findings, the keratitis in this patient was misdiagnosed as a herpes simplex infection. Both viruses cause dendriform lesions, but they usually can be distinguished on morphologic characteristics. Herpes simplex dendrites have a thin ulcerated base and terminal bulbs that stain brightly with fluorescein. Acute zoster dendrites are opaque, broad, and have a raised contour. They are often stellate, and stain sparingly with fluorescein, but prominently with rose bengal.

Unlike herpes simplex virus, which can be isolated readily from corneal scrapings, herpes zoster virus can be cultured from the cornea of immunocompetent hosts only during the first 48 hours after the onset of acute keratitis; attempts to culture virus from delayed or persistent corneal lesions have been unsuccessful.[2] In this case, herpes zoster virus was readily cultured from corneal scrapings taken 11 weeks after the onset of keratitis, which suggests that the immunodeficiency of AIDS may allow persistence of active viral disease.

Differentiation of herpes zoster from herpes simplex lesions is important therapeutically. Topical corticosteroids, used frequently to treat zoster ophthalmicus, are contraindicated in herpes simplex epithelial keratitis. Topical idoxuridine and trifluridine, used for the treatment of herpes simplex keratitis, seem to be ineffective for herpes zoster infections.

Although the keratitis did not respond to systemic acyclovir, it did resolve with acyclovir ointment. This drug has been reported to be superior to topical corticosteroids for treating zoster keratouveitis in immunocompetent patients, by decreasing the duration of disease and the recurrence rates.[3] Punctate epithelial keratopathy with irritation is the most commonly reported complication of therapy and was the only side effect noted in this patient.

Herpes zoster infections may have important diagnostic and prognostic implications. There is a strong correlation between zoster ophthalmicus and the presence of antibodies against human immunodeficiency virus in otherwise healthy-appearing young adults.[4] Furthermore, the occurrence of zoster lesions in patients with

human immunodeficiency virus infection appears to predict an increased incidence in the subsequent development of AIDS.[5]

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Right and Left Views in Radiology

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Most physicians study radiographs as if they were facing the patient. Thus, in observing coronal views, the patient's right is to the observer's left. In dealing with transverse body section images and axial head views, the same relationship is preserved if the images are viewed as if from below (with anterior structures at the top of the image).

In 1976, radiologists at the International Symposium on Computerized Tomography recommended that all axial and transverse computed tomographic scans be viewed as if the body were observed from below. Subsequently, the executive committees of the Society of Neuroradiologists and the American Institute of Ultrasound in Medicine, as well as the editors of Radiology and the American Journal of Roentgenology, made a similar recommendation.[1,2]

Although it is now virtually universal in all fields of medicine to display x-rays, ultrasound images, computed tomographic scans, and magnetic resonance imaging scans with the patient's right to the observer's left, the ophthalmic literature continues to display these views in random fashion.[3-5] Not only are radiologic inconsistencies found within the same issue of a journal, but often inconsistencies appear within a given article.[6]

One can perhaps understand a hesitancy to conform to the 1976 recommendations, because the original orientation advised viewing the brain from above. There is, however, no precedent for viewing coronal scans with the right side of the patient on the observer's right. This practice persists even though it is considered inappropriate to display anteroposterior x-rays of a patient in this way.[7]

It is time for ophthalmologists to adopt the same uniform standards that other physicians have. The only way for this to happen is for the editors of the various ophthalmic journals and basic and clinical science course texts to require that axial and coronal views meet the same uniform standards already adopted by others.

Let us end this radiologic dyslexia and get in step with the rest of the medical community.

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Biodegradability of the Krupin-Denver Valve

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In neovascular glaucoma the anterior chamber angle is irreversibly occluded by proliferative fibrovascular tissue. The prognosis for useful vision with conventional medical and surgical management remains poor. Increased knowledge of the causes of bleb failure and advances in polymer technology have led to a resurgence of interest in the development of setons, aiming to control intraocular pressure permanently in this condition. One such successful seton is the Krupin-Denver valve.[1]

The valve consists of three major components: an extraocular Silastic tube containing horizontal and vertical slits; an open nylon-6 (Supramid) intraocular tube with an internal diameter of 0.88 mm and uniform walls of 0.10 mm thickness; and two horizontal nylon-6 arms. The Silastic tube functions as a undirectional, pressure-sensitive valve and is designed to maintain intraocular pressure between 11 mm Hg and 14 mm Hg. The Silastic tube is molded at a 160-degree angle to the nylon-6 tube, and is trimmed during surgery to extend 1 to 4 mm into the anterior chamber. The two horizontal nylon-6 arms are attached to the undersurface of the junction between the two tubes, and are used for fixation.

Complications from the use of the Krupin-Denver valve include hyphema, ciliochoroidal detachment, external bleb failure, posterior valve migration, granulation tissue ingrowth around the valve, and erosions of the scleral flap and conjunctiva.[2] To this list we add evidence of significant biodegradation of the seton.

A 63-year-old man with neovascular glaucoma had undergone placement of a Krupin-Denver valve in his left eye two years previously after a branch retinal vein occlusion. The valve, which had been placed according to the standard protocol, was guarded by a partial-thickness scleral flap. The tube became occluded by granulation tissue and cryotherapy was necessary to control the intraocular pressure. Visual acuity was reduced to 20/200. Both the scleral flap and the conjunctiva later became eroded. A narrow band of vessels derived from the limbal vessels surrounded the basal part of the intraocular nylon-6 tube.

When perforation of the attenuated overlying conjunctiva appeared imminent, removal of the valve was attempted under retrobulbar anesthesia. The fibrous episcleral capsule was divided and gentle retrograde traction applied to the Silastic segment. The nylon-6 tube separated at its midpoint, however, leaving the distal end tenuously adherent to the iris and in danger of displacement into the vitreous. Its immediate intraocular removal was necessary.

Scanning electron microscopy showed the midportion of the nylon-6 segment to be diffusely attenuated, fractured, and infolded (Fig. 1). The Silastic valve was normal. When compared to a sectioned, unused Krupin-Denver valve (Fig. 2), which showed the nylon-6 tube

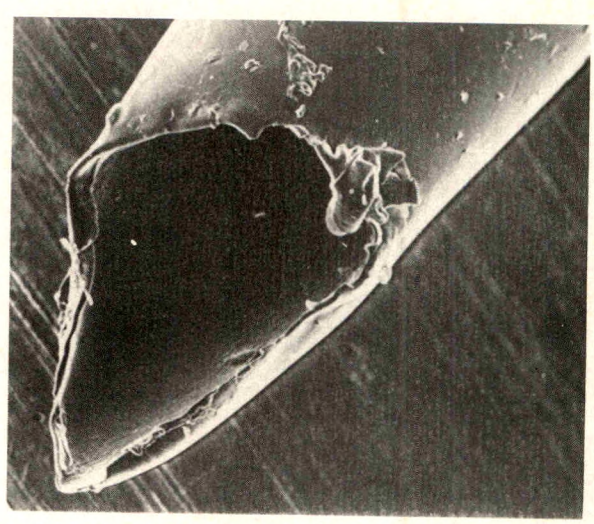


Fig. 1 (Ormerod, Pickford, and Baerveldt). Scanning electron micrograph showing diffuse attenuation of the proximal fracture margin in the nylon-6 part of the Krupin-Denver valve (×63.3).

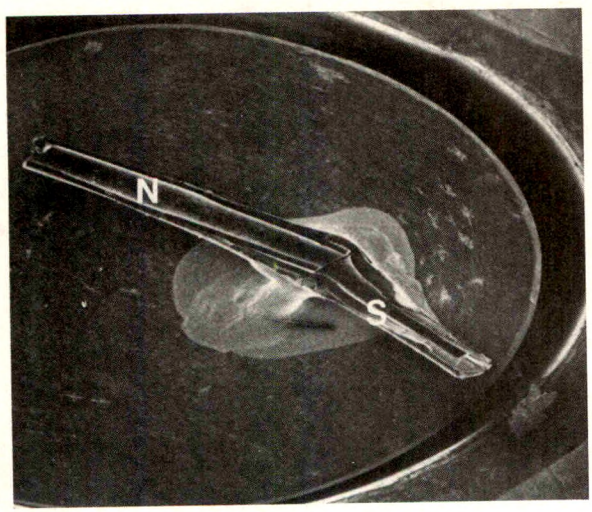


Fig. 2 (Ormerod, Pickford, and Baerveldt). Scanning electron micrograph of a sectioned, unused (untrimmed) Krupin-Denver valve placed in embedding medium (×8.6). N, nylon-6 tube; S, Silastic tube and valve.

to have walls of even thickness (0.1 mm), the nylon-6 tube in this case had undergone both serious biodegradation and loss of tensile strength after two years in the anterior chamber. The ophthalmic biodegradability of nylon-6, used as sutures and intraocular lens loops, has been widely reported[3,4] and reviewed.[5] The use of nylon-6 in the Krupin-Denver valve may lead to its late mechanical failure, and surgeons removing this tube should be alert to the possibility of fracture.

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Chiasmal Compression Caused by a Catheter in the Suprasellar Cistern

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In 1977, Coppeto and Gahm[1] reported a case in which chiasmal compression was caused by a ventricular catheter that had inadvertently lodged in the third ventricle. We treated a patient with progressive visual loss and bitemporal visual field defects caused by a Silastic catheter in the suprasellar cistern.

A 73-year-old woman developed ataxia and "dizziness." Computed tomography disclosed an extra-axial posterior fossa mass and ventricular enlargement. A craniotomy was performed and a large meningioma was resected. An intraventricular catheter was placed and attached to an Ommaya reservoir, for the possibility of conversion to a ventriculoperitoneal shunt, if necessary. The patient did well in the following year, except for progressive left temporal visual field disturbance.

On neuro-ophthalmic examination, best corrected visual acuity was R.E.: 20/30 and L.E.: 20/40. There was a distinct bitemporal hemichromatopsia. Results of a visual field examination disclosed relative bitemporal visual loss in the central isopters. A left afferent pupillary defect was noted. The optic disks were normal.

Postoperative computed tomography showed that the distal end of the supposed intraventricular catheter was located at the level of the suprasellar cistern (Figure). The catheter was subsequently excised.

On follow-up examination two months later, best corrected visual acuity was R.E.: 20/20 and L.E.: 20/25. A questionable left afferent pupil defect was noted. Results of a visual field examination were nearly normal on the right, and showed a diminished temporal scotoma on the left.

Chiasmal compression may occur when a catheter intended for the lateral ventricle inadvertently lodges in the third ventricle or in the suprasellar cistern. The posterior notch of the optic chiasm anatomically forms the anteroinferior border of the third ventricle. The nasal

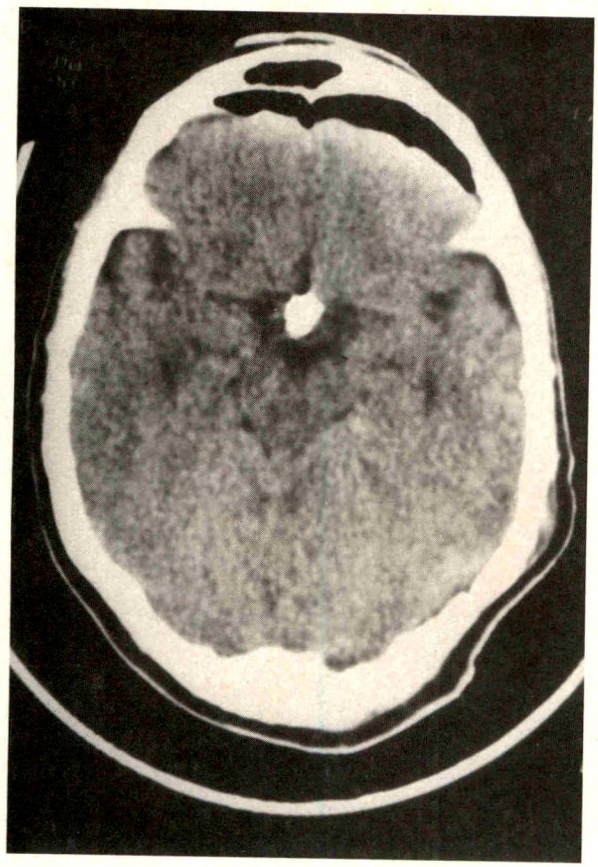


Figure (Slavin and Rosenthal). Computed axial tomogram showing the distal end of the Silastic catheter in the suprasellar cistern.

macular axons from each eye decussate posteriorly in the optic chiasm.[2] Compression of the axons may lead to bitemporal hemianopic scotomas. Corbett[3] described a case in which a misplaced ventricular shunt tube caused total uniocular blindness. The catheter tip was adjacent to the optic canal on computed tomography.

Chiasmal compression may rarely occur because of an associated hydrocephalus caused by a posterior fossa mass lesion.[4] Hydrocephalus may also cause progressive visual loss from chronic papilledema[3] and secondary optic atrophy.

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Foveal Densitometry in the Multiple Evanescent White-Dot Syndrome

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The multiple evanescent white-dot syndrome is a well-defined condition, first described in 1984.[1] Electroretinographic studies during the active stage suggested impaired photoreceptor function with reduced effective visual pigment density and abnormal visual pigment regeneration.[2] Primarily, the retinal pigment epithelium seems to be affected, which results in a reversible metabolic dysfunction with a secondary disturbance of the overlying sensory retina.[2,3] A more recent report did not confirm electroretinographic abnormalities in all patients.[3]

Recently, we had the opportunity to perform foveal densitometry and color matching during the active and recovery stages of the multiple evanescent white-dot syndrome in a patient with normal electroretinographic findings.

A 20-year-old woman had a four-day history of blurred vision in the right eye. Informed consent was obtained after the aims of the study were carefully explained. She was in good health, without viral-like symptoms. Her visual acuity was R.E.: 20/40 and L.E.: 20/13. Slit-lamp biomicroscopy showed no abnormalities. Ophthalmoscopy of the right eye disclosed characteristic tiny white dots clustered in the perimacular area, beyond the vascular arcades and nasal to the optic disk. The dots appeared to be located deep in the sensory retina or at the level of the retinal pigment epithelium. Retinal pigment epithelial granularity was noted at the fovea. The optic

disk showed slight edema. The left eye was normal. Fluorescein fundus angiography confirmed the diagnosis,[1] and showed a slight leakage in the macular area. Results of electroretinography and electro-oculography were normal. Static perimetry of the right eye disclosed a relative central defect of 7 dB. Color vision testing with a Nagel anomaloscope showed an obvious pseudoprotanomaly (mean match, 52 ± 2 S.D.; normal range, 42 ± 2 S.D.). Results of a Farnsworth Panel D-15 test and Ishihara and Hardy-Rand-Rittler tests were normal. Foveal densitometry with the Utrecht retinal densitometer[4] on the preferred, foveal fixating point of the right eye demonstrated a profound disturbance of cone photopigment kinetics. The density difference between fully dark-adapted and fully bleached was 0.05 (normal mean, 0.32 ± 0.03 S.D.) with a strongly increased time constant of pigment regeneration of 218 ± 77 seconds (normal mean, 99 ± 10 seconds). Laboratory serum tests did not show increased serum levels of total IgG and total IgM, as reported recently.[5] Results of serum tests of IgA, C3, C4, C-reactive protein, VDRL, antinuclear antibody, rheumatoid factor, HLA-B27, *Toxoplasma*, erythrocyte sedimentation rate, and IgM of herpes zoster and herpes simplex were negative. Immunofluorescence of herpes simplex IgG was 1:64 and varicella zoster was >1:1,024.

Within two weeks after the patient's first visit, visual acuity was R.E.: 20/20. The density difference had improved to 0.12 and the time constant of pigment regeneration was 98 ± 19 seconds. The pseudoprotanomaly was less obvious (mid match, 48 ± 5 S.D.). Results of an electroretinogram and an electro-oculogram were normal. Four weeks after the first visit, visual acuity was R.E.: 20/16. Examination of the fundus showed perifoveal retinal pigment epithelium granularity. The dots had completely disappeared. The density difference remained 0.12, and the time constant was 84 ± 19 seconds. Static perimetry showed a relative central defect of 2 dB and a mid match of 45 ± 2 S.D. was noted on anomaloscopy. On fluorescein fundus angiography the optic disk edema had obviously decreased. No macular leakage was observed, although some window defects were noted. With regard to the granularity, these defects were less than expected. Eight weeks after onset, visual acuity was R.E.: 20/13; results of color vision tests, visual fields, and densitometric registration were within normal limits. Immunofluorescence of herpes simplex IgG was negative and varicella zoster IgG was 1:1,024.

In conclusion, we confirmed by retinal densitometry that in the multiple evanescent white-dot syndrome, gross abnormalities exist during the active stage at the level of the cone photoreceptor outer segments, even with normal electroretinographic findings. This has been suggested in cases with abnormal electroretinographic findings. The anomaloscopic results corroborate these results. The low density and increased time constant of pigment regeneration during the active stage, together with a slight leakage of dye in the macula on fluorescein angiography, confirm the proposed model of transient metabolic disturbance at the level of the pigment epithelium-photoreceptor complex.

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Brown's Syndrome in Twins

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The superior oblique tendon syndrome, a motility defect manifested by a deficiency of

elevation of the adducted eye, was originally described by Brown[1] in 1950. Katz, Whitmore, and Beauchamp[2] reported a case of Brown's syndrome in monozygotic twin girls. Although evidence of genetic influence in Brown's syndrome is scant, scattered case reports suggest that it may be transmitted by an autosomal dominant gene with variable penetrance.[3]

We examined monozygotic twin girls at 2¾ years of age. On examination, the first twin had a right esotropia of 40 prism diopters, absence of elevation in adduction of the right eye, and right amblyopia. Results of examination of the second twin showed mirror imaging of the same symptoms. She had a left esotropia of 40 prism diopters, absence of elevation in adduction of the left eye, and left amblyopia (Figure). Although born six weeks prematurely, both girls had normal refractive errors for their age. There was no history of ocular or birth trauma, and no family history of strabismus. Results of laboratory studies of the ABO, Rh, MNS, and Lewis blood group systems from both the twins and their parents disclosed a 97% probability that these twins are monozygous.

A combined superior oblique muscle tenotomy and an inferior oblique muscle recession was performed on the involved eye of each girl. Intraoperatively, limitation of elevation in adduction was noted in the involved eye of each child. No other abnormality of duction was found.

Brown subdivided this condition into true and simulated syndromes. True (congenital) Brown's syndrome includes only those cases that have a congenitally short anterior sheath of the superior oblique tendon. Simulated Brown's syndrome includes all cases with features similar to those of the true group. Both are further classified as spontaneous recovery cases, intermittent cases, and acquired cases.[4] It is now agreed that most of true Brown's syndrome cases result from a tight superior oblique tendon.[5]

The cause of the mirror imaging in our patients is not certain. It is highly unlikely that a gestational insult occurred before monozygotic cleavage. This insult would have to have been instantaneous, approximately two weeks in gestation, and well localized to have affected only the superior oblique muscle complex. We believe that this case provides further evidence of a genetic basis for some cases of Brown's syndrome.

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Figure (Wortham and Crawford). Brown's syndrome in monozygotic twins. Note the absence of elevation of the outer eye in each twin.

Cartilagenous Choristoma of the Eyelid Tarsus

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Cartilage in the orbit is usually found only at the trochlea. Bowen and associates[1] reported a case of a cartilagenous hamartoma of the orbit.

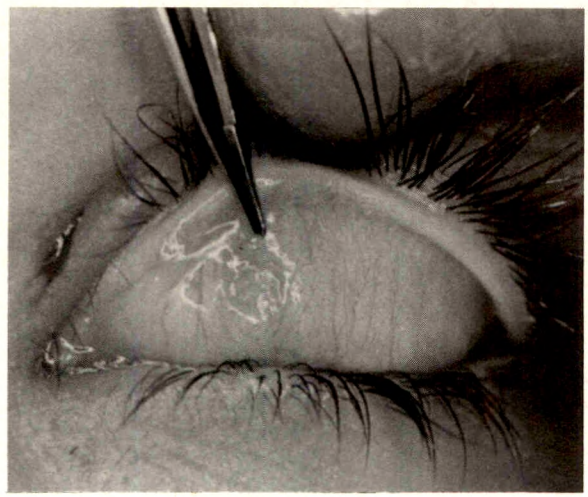


Fig. 1 (Mauriello, Voglino, and Otazo). Appearance of the lesion on eversion of left upper eyelid.



Fig. 2 (Mauriello, Voglino, and Otazo). Chondrocytes are present within the cartilagenous choristoma (hematoxylin and eosin, ×300).

Others[2-4] have reported simple and complex (more than one choristomatous tissue) choristomas of the epibulbar surface.

An 11-year-old girl developed a 1-mm mass in the medial aspect of the left upper tarsus. Although there was no history of inflammation, the working diagnosis was chalazion. Excisional biopsy of the mass through a small skin incision showed hyaline cartilage. The lesion gradually recurred over a two-year period and was slightly larger than its original size. The patient was referred to one of us (J.A.M.) for further evaluation.

Results of an ocular examination disclosed a firm, somewhat irregular recurrent mass that was palpable through the skin at the medial aspect of the tarsus. Eversion of the eyelid showed that the mass was within the tarsus (Fig. 1). The mass was excised using a conjunctival approach. It was found to be intratarsal and extended minimally into the overlying orbicularis muscle. There was no recurrence of the mass after one year.

Microscopy of both the original lesion and the recurrent mass showed mature chondrocytes in a fibrous matrix. The specimens were identified as nodular islands of hyaline cartilage (Fig. 2).

Although cartilage and bone may be found in scleral tissues of fish, amphibians, reptiles, and birds,[5] such findings in human scleral tissues are rare.[1-4] Since cartilage is not normally present in human eyelid tissues, we have classified this lesion as a choristoma. The origin of the growth is presumably primitive mesoderm, which also gives rise to the tarsus.

ACKNOWLEDGMENT

Lorenz E. Zimmerman, M.D., Department of Ophthalmic Pathology, Armed Forces Institute of Pathology, Washington, D.C., reviewed the slides of both the original lesion and the recurrent mass.

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Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Sulfur Hexafluoride Gas in the Repair of Intractable Descemet's Membrane Detachment—Correction

EDITOR:

In our Letter to the Journal, "Sulfur hexafluoride gas in the repair of intractable Descemet's membrane detachment" (Am. J. Ophthalmol. 104:660, December 1987), two errors occurred during the editorial process.

The second sentence in the last paragraph on page 661 should read "In managing this case, we tried unscrolling Descemet's membrane with a spatula, full-thickness corneal fixation sutures and reapproximation with air, but the large Descemet's membrane detachment persisted." The sentence that begins on the third line of page 662 should read, "We then tried a new technique: injection of 20% sulfur hexafluoride gas, which does not expand,[3] but lasts longer than air in the eye."

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Atlanta, Georgia

Vitrectomy Surgery in Proliferative Sickle Retinopathy—Correction

EDITOR:

Further examination of Patients 2 and 3 described in our article, "Vitrectomy surgery in proliferative sickle cell retinopathy" (Am. J. Ophthalmol. 104:133, August 1987), documents hemoglobin SC disease, and not SS disease as previously noted.

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BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Walsh and Hoyt's Clinical Neuro-Ophthalmology, ed. 4, vol. 3. Ocular, Orbital and Intracranial Tumors and Related Conditions. By Neil R. Miller. Baltimore, Williams and Wilkins, 1987. 1870 pages, index, illustrated. $102

Reviewed by NANCY NEWMAN
San Francisco, California

This is the third volume of a projected five volumes in the fourth edition of Walsh and Hoyt's Clinical Neuro-Ophthalmology. The first two volumes covered the visual sensory system; the optic nerve; the autonomic nervous system; pupillary function; accommodation and lacrimation; the oculomotor system: embryology, anatomy, physiology, and topographic diagnosis; and the sensory innervation of the eye and orbit. It is projected that volume 4 will cover vascular disease and trauma and that volume 5 will be concerned with inflammatory, infectious, and functional disease.

This volume contains 11 chapters, which cover the following in order: neuro-ophthalmic topographic diagnosis of tumors and related conditions; tumors of neural ectodermal origin; tumors of the meninges and related tissues; meningiomas and sarcomas; tumors of maldevelopmental origin and related lesions; tumors of the pituitary gland; tumors and hamartomas of blood vessels; tumors of cranial and peripheral nerves; tumors involving hematopoietic cells and tissue; miscellaneous tumors of neuro-ophthalmic interest; paraneoplastic syndromes; and the phakomatoses.

As we have come to expect from Dr. Miller, this is a comprehensive compilation of a wealth of clinical and pathologic material. Of necessity, because of the nature of the topics, there is a good deal of repetition and Dr. Miller has had to make some choices where conflicts exist among experts vis-a-vis terminology and classification. This he has done even-handedly and, from a clinician's viewpoint, effectively.

Many details are better tended to than in earlier volumes. The paper has been consistently upgraded and the typographical and computer errors are negligible in this volume. In particular, the index is much more inclusive (but still could be improved). The magic of computer enhancement has improved the quality of many of the figures taken from earlier texts, in particular, Russell and Rubinstein's "Pathology of Tumors of the Nervous System" and Dr. Rubinstein's "Tumors of the Central Nervous System." The lavish use of appropriate illustrations is a significant plus for this volume.

This volume, like the others in the series, probably will be the "gold standard" until Dr. Miller revises it. It is a must for those with an abiding interest in the topics covered, all medical, ophthalmologic, neurologic, neurosurgical, and pathology libraries and it will be a welcome resource for clinicians and researchers in many other disciplines because of its coverage of the endocrinologic aspects of pituitary tumors, the phakomatoses, paraneoplastic syndromes, and other topics with ramifications in many branches of medicine. Bravo! Dr. Miller.

Surgery of the Eye, two volumes. Edited by Stephen R. Waltman, Richard H. Keates, Creig S. Hoyt, Bartley R. Frueh, Jonathan Herschler, and Denis M. Carroll. New York, Churchill Livingstone, Inc., 1988. 1111 pages, index, illustrated. $240

Reviewed by E. MICHAEL VAN BUSKIRK
Portland, Oregon

This text provided a monumental task for the publishers and six principal editors: to collect the works of the 71 contributing authors over the broad scope of ocular surgery. Their task was to preserve consistency in format, quality, and scope, while avoiding duplication and serious deletion. The editors have compiled a generally excellent and complete text that will serve its readers admirably as a thorough reference for the entire spectrum of ocular surgery, from adjustable sutures to Z-plasty. Like any multiauthored endeavor, some chapters outshine others, but the majority speak with authority and provide state-of-the-art guidelines to the performance of each procedure. The sections are well organized, progressing from routine and mundane procedures to more complex and unusual ones. Handsomely boxed as a two-volume set, Surgery of the Eye should

serve as a useful and convenient reference that surgeons will want to review before approaching an uncommonly performed operation or when contemplating what may be in store for the patient with extraordinarily complex or unusual disorders.

This is not strictly a "how to" manual for routine eye surgery, but a useful introduction for the beginning eye surgeon, which discusses indications and perspectives as well as the various procedures. It does not, however, provide sufficient detail to serve the prospective surgeon as the only guide through every procedure. Entire books have been written about some of the topics addressed in many of the chapters. Future editions should include an introduction or an opening chapter devoted to some of the general principles of ocular surgery, such as the handling of delicate instruments, the grasping, cutting, and suturing of ocular tissue, and intraocular pressure dynamics during ocular surgery.

The highly personal tone of the text provides charm and character, as well as authority. Such a personal approach could risk substituting timeless principles with contemporary fads. It demands that the editors separate trendy soothsaying from relevant controversy, and they have met these demands. Most aspects of ocular surgery receive a balanced perspective, which provides the reader with a valuable reference and contemporary view of ocular surgery.

Surgery of the Eye provides a broad and thorough reference for ocular surgeons in which both residents and graduate ophthalmologists will find authoritative descriptions of contemporary surgical management.

Primer of Biostatistics. The Program. By Stanton A. Glantz. Computer disk with instructions for use. New York, McGraw-Hill Book Co., 1988. $35

Reviewed by JONATHAN C. JAVITT
Baltimore, Maryland

Over the past years, clinical research has evolved to the point where most papers submitted for publication in the ophthalmic literature require some degree of statistical analysis of the data. While large studies requiring complex multivariate analysis generally require the participation of a statistician for data analysis, it is often impractical to engage a biostatistician every time one needs to perform a *t*-test or chi-square analysis. Although there are a number of excellent statistical programs designed to run on microcomputers, they tend to cost several hundred dollars and often require fair knowledge of biostatistics. None of the traditional packages teach the user how to analyze data. Moreover, these packages often require establishing a database for each study, which can be time consuming.

Many clinical investigators continue to turn to the statistics textbook and a calculator for their daily needs. For many years, Dr. Glantz's Primer of Biostatistics has served as an invaluable resource to the clinician in need of basic statistical techniques.

Combined with the second edition is a menu-driven software package that will run on any IBM-compatible computer. The minimum computer configuration is a floppy disk drive and 256K of memory. The program will support a math co-processor (8087 or 80287) for faster calculations if the computer is so equipped. A Macintosh version of the software is expected in May 1988. Unprecedented and long overdue, this product contains the clarity of writing of a book, is sold through bookstores by a book publisher, and is offered at a book price. In addition to the well documented manual, the program itself will assist the user in choosing the appropriate test based upon the type of data being analyzed. As such, it serves as a clever teaching tool in addition to its analysis functions.

The book is organized into well-illustrated sections that cover descriptive statistics, techniques for comparing two or more groups, methods for analyzing rates and proportions, and basic techniques for analyzing treatment outcomes and assessing confidence limits. Each type of analysis is accompanied by an example from an actual clinical study. Exercises are offered at the end of each chapter with answers at the back of the book. The only criticism of the primer is that, although statistical tables are interspersed throughout the text as the corresponding test is discussed, they are not available in an appendix for quick access.

The addition of the software program makes those standard tables obsolete, however. The diskette as supplied ran flawlessly. Upon typing "PRIMER" at the prompt on my computer, I was instantly presented with a menu listing the various analyses available. If the user chooses the "recommend test" option, the pro-

gram will ask a series of questions about the type of data being analyzed and then suggest the most appropriate test.

The program runs all of the basic statistical tests described in the book and does so in the most straightforward possible manner. For each test, one has the option of entering the raw data or reading a file that is easy to prepare with any standard word processor. Many tests will allow the user to enter the means, standard deviations, and other characteristics of the sample group, rather than each data point.

This software is not designed to perform complex multivariate analyses, or handle any data set larger than 200 data points. These are tasks best left to more powerful database and statistical packages that require some statistical expertise. I was able to perform *t*-tests and other comparative statistics on a study with two groups of 50 patients each in less than ten minutes. The same task would have taken considerably more time on a full fledged microcomputer or mainframe statistical package. At a price much more consistent with a textbook than a software package, Primer of Biostatistics is an invaluable addition to the armamentarium of any clinical investigator.

Diabetes and Its Ocular Complications. By William E. Benson, Gary C. Brown, and William Tasman. Philadelphia, W. B. Saunders Company, 1988. 216 pages, index, illustrated. $65

Reviewed by MATTHEW D. DAVIS
Madison, Wisconsin

This comprehensive review of the ocular complications of diabetes by three outstanding ophthalmologists with broad experience in this area will be a welcome addition to any ophthalmic library. The first third of the text reviews the epidemiology of diabetic retinopathy and theories regarding its pathogenesis. Also included here are chapters on psychophysical and electrophysiologic abnormalities and on the blood retinal barrier. The second major section of the book deals with the clinical findings, differential diagnosis, and course of retinopathy, and with nonretinal ocular complications as well. The final section considers treatment and concludes with a chapter on histopathologic findings by David Apple and associates.

Each chapter reviews much of the voluminous relevant literature, and provides both a useful summary of current opinions and a guide for those wishing to pursue any specific area in greater depth. Perhaps of greatest value to ophthalmologists involved in the treatment of diabetic retinopathy will be the practical suggestions regarding management derived from the authors' extensive clinical experience.

Uveitis. A Colour Manual of Diagnosis and Treatment. By Jack J. Kanski. Stoneham, Massachusetts, Butterworths, 1987. 114 pages, index, illustrated. $59.95

Reviewed by WILLIAM W. CULBERTSON
Miami, Florida

This is a beautifully illustrated and concise handbook, which could serve as a handy reference source for ophthalmologists dealing with frustrating cases of uveitis. An excellent introductory chapter orients the reader to the various classifications, schemes, and general clinical features of uveitis. This is followed by chapters on uveitis associated with arthritis, noninfectious systemic diseases, and chronic systemic infections. Subsequent chapters deal with parasitic, viral, and fungal infections and "idiopathic specific uveitis entities." The book concludes with three chapters on the general medical management of uveitis and surgery for complicated cataracts and secondary glaucomas.

Probably the most worthwhile features of the book are Dr. Kanski's interspersed clinical notes and the excellent diagrams and clinical photographs that illustrate each type of uveitis. The sections on toxoplasmosis and juvenile rheumatoid arthritis are especially well written and illustrated. Techniques for performing procedures such as chelation of band keratopathy, periocular corticosteroid injections, and pars plana lensectomy are described in a helpful, practical manner.

The manual would be of even greater practi-

cal assistance to ophthalmologists if more specific details of treatment (doses, end points of treatment, and the like) were included. An additional chapter describing the systematic workup of patients with unknown types of uveitis would have been useful in this otherwise comprehensive book.

Books Received

Ophthalmology Annual 1988. Edited by Robert D. Reinecke. New York, Raven Press, 1987. 256 pages, index, illustrated. $73

Dr. Reinecke's series of "Annuals" has developed into a collection of valuable reviews of small topics. These clear, instructional reviews should have a large readership. There are many ophthalmologists around the world eager to learn what's new in modern eye care. If this volume were translated into Spanish or Chinese, for example, I expect it would be highly valued.

The Ocular Fundus. Methods of Examination and Typical Findings, ed. 5. By Arno Nover. Translated by Frederick C. Blodi. Stuttgart, Germany, F. K. Schattauer, 1987. Softcover, 197 pages, index, illustrated. $50

The fifth edition, with minor changes from the fourth edition, is now available in softcover. As before, the fundus pictures are crystal clear.

Contact Lens Perspectives. By Richard M. Hill. New York, Professional Press Books, 1988. 112 pages, illustrated. $22.50

Another small book by the author of "Curiosities of the Contact Lens." This one should also be popular. It will be a good source of basic information about contact lens wear for residents in ophthalmology. Each of the 30 short chapters has a catchy title and many clear graphs of uniform design.

Primary Eye Care in Developing Nations. By Larry Schwab. New York, Oxford University Press, 1987. 203 pages, softcover, index, illustrated. $9.95

This is a simple guide to the practical management of severe eye disease under difficult conditions. It is aimed at medical assistants and general physicians in remote parts of the world who must get along with limited supplies and the simplest equipment. It is an altogether admirable little book whose very existence and availability should help to prevent a lot of blindness.

Optics for Ophthalmologists. By Alfredo A. Sadun and James D. Brandt. New York, Springer-Verlag New York, Inc., 1987. Softcover, 104 pages, illustrated. $19.95

This clear workbook for ophthalmology residents who want to understand ophthalmic optics is complete with problems to work, multiple choice questions, and a "crib" sheet.

A Manual of Visual Anatomy and Physiology. By Harry J. Wyatt. New York, Professional Press Books, 1988. Softcover, 218 pages, illustrated. $20

This laboratory manual for students offers a brief overview of the anatomy and physiology of the visual system as seen through the author's own "chalk board" diagrams.

The Merck Manual, ed. 15. Edited by Robert Berkow, Editor-in-Chief, and Andrew J. Fletcher, Assistant Editor. Rahway, New Jersey, Merck & Co., Inc., 1987. 2,576 pages, index. $21.50

The Merck Manual still tries to jam as much information as it can into its small format. It is now up to over 2,500 pages and is as popular as ever. The last edition sold 800,000 copies. A two-volume softcover version is available at the same price.

For Our Patients: Diabetic Retinopathy. By Howard Schatz and H. Richard McDonald. San Francisco, The Retina Research Fund, 1988. Softcover, 71 pages, black and white version, $3.00; color version, $15

This clear and informative booklet on diabetic retinopathy joins a similar booklet on macular degeneration by the same authors (AJO, Sept. 1987) in what promises to be an exemplary instructional series.

Obituary

ZACHARIAS DISCHE
1896–1988

Zacharias Dische died at the age of 92 years in New York City, Jan. 21, 1988. He was born in Poland in 1896, served in the Austrian-Hungarian army, and received the M.D. degree from the University of Vienna. He entered the biochemistry laboratory of Professor Fürth and became chief of biochemistry of the Institute of Physiology of the University of Vienna in 1931. He discovered the pentose shunt reaction of intermediary hexose metabolism. In 1938 he went to France where he worked briefly at the University of Marseille and discovered the "feedback mechanism" of the control of enzymatic processes. He then worked at Mount Sinai Hospital, and then the departments of biochemistry and ophthalmology of Columbia University. There he clarified the chemical mechanism of the clarity of the cornea, lens, and vitreous. He discovered a large number of color reactions to identify various sugars. He received the Proctor Medal award of the Association for Research in Ophthalmology on June 9, 1965.

FRANK W. NEWELL

ABSTRACT DEPARTMENT

Edited by David Shoch, M.D.

Anaesthesia

Anaesthesia and septo-optic dysplasia. Sherlock, D. A., and McNicol, L. R. (Royal Hosp. for Sick Children, Yorkhill, Glasgow G3 8SJ, Scotland). Anaesthesia 42:1302, 1987.

Septo-optic dysplasia (De Morsier's syndrome) is a congenital, neurologic disorder that may be the most common cause of optic nerve hypoplasia. Associated with the optic nerve hypoplasia is an absence or abnormality of the septum pellucidum, midbrain anomalies, and hypothalmic/pituitary dysfunction. There may be orthopedic deformities and hypotonia. Afflicted children are subject to seizures particularly after general anesthesia. Children of abnormally small stature, with defective vision, spasticity, and a history of seizures, should be carefully monitored for optic nerve hypoplasia before undergoing any surgical procedure. Perioperative corticosteroid therapy and prevention of hypoglycemia may be required. (1 figure, 1 table, 5 references)—David Shoch

Australian and New Zealand Journal of Ophthalmology

Survival of corneal endothelium in McCarey-Kaufman (M-K) medium subjected to agitation. Robertson, I. F., Carrol, N., Brooks, A. M. V. (82 Collins St., Melbourne, 3000, Australia). Aust. N.Z. J. Ophthalmol. 15:303, 1987.

Human corneas were bisected and each half placed in McCarey-Kaufman medium. One was agitated mechanically and the other was kept stationary. Scanning electron microscopy showed no difference in endothelial structure. The results are significant since some donor corneas are now transported long distances. (7 figures, 3 references)—Ronald F. Lowe

Computer-aided volume measurement of choroidal melanomas. Gosbell, A. D., Barry, W. R., and Favilla, I. (15 Collins St., Melbourne, 3000, Australia). Aust. N.Z. J. Ophthalmol. 15:349, 1987.

Using a combination of conventional B-scan ultrasonography, standard video techniques, computer image digitization, and area analysis, it is possible to measure the volume of choroidal melanomas by area calculation of successive ultrasound image slices, thus allowing the monitoring of such tumors. This study described the design of a combined water-bath and linear tracking B-scan transducer together with the instrumentation and computer software required. The results of volume measurements performed upon eye models demonstrated that melanomas of volume greater than 100 mm^3 could be measured with an average error of 6%. (19 figures, 13 references)—Ronald F. Lowe

British Journal of Ophthalmology

Morphological changes in the human corneal epithelium associated with surgical corneal clouding. Hague, S., Dilly, N., and Thompson, G. M. (Dept. Ophthalmol., St. George's Hosp., Blackshaw Rd., London SW17 OQT, England). Br. J. Ophthalmol. 71:729, 1987.

In this study the authors removed small specimens of the peripheral corneal epithelium from ten patients undergoing surgical procedures. Seven patients had extracapsular lens extractions with a lens implant, two had extracapsular extractions, and one had a lens aspiration. They found no correlation between corneal clouding and preoperative medications, operative fluids used, or duration of surgery. Care was taken not to injure the cornea with any solutions used to sterilize the fornices.

Corneal clouding could not be prevented by simple instillation of saline on the cornea. The authors concluded that the major cause of epithelial clouding in intraocular surgery is damage to the endothelium and interference with the pump mechanism. There appears to be a correlation between the degree of corneal clouding and the use of closed intraocular infusion during surgery. (8 figures, 7 references)—David Shoch

Intraocular reticulum cell sarcoma: diagnosis by choroidal biopsy. Kirmani, M. H., Thomas, E. L., Rao, N. A., and Laborde, R. P. (Estelle Doheny Eye Foundation, USC School of Med., 1355 San Pablo St., Los Angeles, CA 90033). Br. J. Ophthalmol. 71:748, 1987.

Reticulum cell sarcoma manifests in the eye as a chronic uveitis that does not respond to the usual corticosteroid therapy. The diagnosis can often be made by vitreous biopsy. In the patient described a pars plana vitrectomy failed to detect reticulum cell sarcoma. Results of further physical examination were within normal limits, and there was no evidence of any enlarged lymph nodes or lacrimal glands. Other forms of cancers were ruled out as well. It was decided to perform a choroidal biopsy and this was done through a scleral window. Histologic examination confirmed the diagnosis of reticulum cell sarcoma. The patient was treated with external beam radiation, and methotrexate was given intrathecally at weekly intervals for one month. Transscleral choroidal biopsy is indicated in patients with negative vitreous biopsy results and strong clinical evidence for this usually fatal lymphoma. (8 figures, 25 references)—David Shoch

Contrast sensitivity, acuity, and the perception of 'real-world' targets. Owsley, C., and Sloane, M. E. (Dept. Ophthalmol., School of Med., Eye Foundation Hosp., Univ. Alabama at Birmingham, Birmingham, AL 35294). Br. J. Ophthalmol. 71:791, 1987.

A major assumption underlying the use of contrast sensitivity testing is that it predicts whether a patient has difficulty seeing objects encountered in everyday life. However, there has been no large-scale attempt to examine whether this putative relationship actually exists. The authors examined this assumption using a clinic based sample of adults aged 20-77 years. Contrast thresholds were measured for both: (1) gratings of 0.5-22.8 cycles/degree; and (2) real-world targets (faces, road signs, objects). Multiple regression techniques indicated that the best predictors of thresholds for real-world targets were age and middle to low spatial frequencies. Models incorporating these variables accounted for 25-40% of the variance. Although acuity significantly correlated with thresholds for real-world targets, the inclusion of acuity as a predictor variable did not improve the model. These data provide direct evidence that spatial contrast sensitivity can effectively predict how well patients see targets typical of everyday life. (2 figures, 5 tables, 17 references)—Authors' abstract

Collagen distribution in the lamina cribrosa and the trabecular meshwork of the human eye. Rehnberg, M., Ammitzboll, T., and Tengroth, B. (Dept. Ophthalmol., Karolinska Inst. and Hosp., S-104 01 Stockholm, Sweden). Br. J. Ophthalmol. 71:886, 1987.

The authors undertook a study to determine the types of collagen present in the sclera compared to the lamina cribrosa. They found that the sclera consists primarily of Type 1 collagen, usually found in tendons and skin. In addition to collagen Type 1, collagen Types 3 and 4 were found in the lamina cribrosa, the trabecular meshwork, and the retrolaminary optic nerve. Type 3 is usually found in blood vessels, whereas Type 4 is found in basement membrane. (4 figures, 1 table, 5 references)—David Shoch

Isolated foveal hypoplasia. Oliver, M. D., Dotan, S. A., Chemke, J., and Abraham, F. A. (Eye Dept., Kaplan Hosp., 76-100 Rehovot, Israel). Br. J. Ophthalmol. 71:926, 1987.

The authors described 15 cases of foveal hypoplasia without any other generalized or ocu-

lar disease. The characteristic findings were normal optic nerve heads; absent or abnormal macular and foveal reflexes; and retinal capillaries, which ran from the upper and lower arcades close to the presumed foveal area. Some of the capillaries crossed the horizontal meridian. Fluorescein angiograms were performed on seven patients. In four there was a lack of macular pigmentation so that the choroidal fluorescence showed through. The diagnosis of isolated foveal hypoplasia should be considered when nystagmus is present without generalized or ocular disease. (4 figures, 1 table, 13 references)—David Shoch

International Journal of Radiation Oncology, Biology, Physics

Radiation therapy for Graves' ophthalmopathy: a retrospective analysis. Palmer, D., Greenberg, P., Cornell, P., and Parker, R. G. (Dept. Radiat. Oncol., UCLA Ctr. for the Health Sci., Los Angeles, CA 90024). Int. J. Radiat. Oncol. Biol. Phys. 13:1815, 1987.

Most patients with Graves' ophthalmopathy can be controlled with large doses of corticosteroids or with orbital decompression. There are patients, however, for whom corticosteroids are contraindicated and who are not good candidates for surgery. Radiation is an alternative therapy for these patients. The authors did a retrospective analysis of 29 patients with Graves' ophthalmopathy. Median follow-up was 49 months. The results were evaluated by three different specialists: a radiation oncologist, an ophthalmologist, and an endocrinologist. They agreed that about 50% of the patients had improved with respect to most signs and symptoms including proptosis. The soft tissue changes were relieved in about 75% of of the patients. In contrast, ophthalmoplegia responded poorly. Of some significance is the finding that 13 patients required surgery for residual signs and symptoms after the radiation therapy. (6 figures, 3 tables, 11 references) —David Shoch

International Ophthalmology Clinics

The epidemiology of diabetic retinopathy: findings from the Wisconsin epidemiologic study of diabetic retinopathy. Klein, R. (Dept. Ophthalmol., 600 Highland Ave., Madison, WI 53792). Int. Ophthalmol. Clin. 27:230, 1987.

An epidemiologic study of more than 10,000 diabetic patients residing in southern Wisconsin showed that despite medical management, nearly all of the younger onset diabetics who take insulin have retinopathy after 25 years of the disease. A high proportion of this group have proliferative retinopathy. Those who develop diabetes later in life do not have as high an incidence of diabetic retinopathy but account for the large proportion of the diabetic persons in any population. Diabetic children have a low risk of retinopathy before puberty. After puberty the risk of retinopathy increases with duration of the disease. The epidemiologic study indicates that increased blood glucose levels and higher blood pressure are associated with the presence and severity of retinopathy. (6 figures, 4 tables, 48 references)—David Shoch

Journal of Ocular Pharmacology

Ganglioside administration in retinitis pigmentosa. Newsome, D. A., Dorsey, F. C., May, J. G., Bergsma, D. R., and Bazan, N. G. (LSU Eye Center, 2020 Gravier, Ste. B, New Orleans, LA 70112). J. Ocular Pharmacol. 3:323, 1987.

The authors evaluated the effectiveness of a daily 40-mg intramuscular dose of ganglioside in individuals with retinitis pigmentosa. The study was performed in a prospective, double-blind, randomized, placebo-controlled trial in 30 subjects with retinitis pigmentosa. The criteria for improvement were visual field area and electroretinographic response amplitudes. When the code was broken it was found there was a marginally statistically significant increase in visual field area in the ganglioside-treated group. For those patients who had a recordable electroretinogram at baseline and received a drug there was an increase in amplitude in three of the five patients. The data recorded here do not warrant the use of ganglioside for treatment at this time but do indicate the possible usefulness of a larger study. (3 tables, 32 references)—David Shoch

Neurology

Cerebral metabolism and patterned visual stimulation: A positron emission tomographic study of the human visual cortex. Kushner, M. J., Rosenquist, A., Alavi, A., Rosen, M., Dann, R., Fazekas, F., Bosley, T., Greenberg, J., and Reivich, M. (Cerebrovascular Res. Ctr., Dept. Neurol., 429 Johnson Pavilion, 36th & Hamilton Walk, Univ. Pennsylvania, Philadelphia, PA 19104). Neurology 38:89, 1988.

The visual cortical metabolic activities of normal, right-handed men, aged 18 to 30 years, were studied by means of positron emission tomography employing a radioactive glucose compound (^{18}F-fluorodeoxyglucose). In general, stimulation of the macular region of either hemifield produced a significant increase in metabolism of the contralateral posterior striate cortex. However, there were highly significant asymmetries in metabolism of the prefrontal and inferior parietal cortices, and metabolic activation in extrastriate areas was greater on the right side. This study confirmed that the right hemifields are represented in the left visual cortex and vice versa. What has not been noted previously is that the right cerebral hemisphere may be specialized for visual processing. (3 figures, 3 tables, 38 references)—David Shoch

Magnetic resonance imaging of the optic nerve in optic neuritis. Miller, D. H., Newton, M. R., van der Poel, J. C., du Boulay, E. P., Halliday, A. M., Kendall, B. E., Johnson, G., MacManus, D. G., Moseley, I. F., and McDonald, W. I. (Inst. Neurol., Queen Sq., London WC1N 3BG, England). Neurology 38:175, 1988.

Magnetic resonance imaging, which has been useful in detecting lesions in the brain of patients with multiple sclerosis, has not been as useful in imaging the optic nerve in optic neuritis because of interference from the orbital fat. The problem appears to be a high proton density and a short T_1-relaxation time in orbital fat. The authors used a new sequence, which they term STIR, for short inversion time inversion recovery sequence. Using this sequence the authors were able to detect abnormalities in the symptomatic nerve in ten of 14 patients with acute unilateral optic neuritis. However, visual-evoked potentials were even more sensitive than magnetic resonance imaging in detecting lesions. Therefore, rather than magnetic resonance imaging the authors recommend visual-evoked potentials as the investigation of choice in suspected demyelinating disease involving the optic nerve. 4 figures, 4 tables, 29 references)—David Shoch

Risk of developing multiple sclerosis after uncomplicated optic neuritis: a long-term prospective study. Rizzo, J. F., and Lessell, S. (Massachusetts Eye and Ear Infirm., 243 Charles St., Boston, MA 02114). Neurology 38:185, 1988.

The incidence of developing multiple sclerosis after uncomplicated optic neuritis seems to vary with the criteria used for the diagnosis both of optic neuritis and multiple sclerosis. To overcome this variability the authors used previously described standards to divide their patients into three categories: definite, probable, or possible multiple sclerosis. The total group studied prospectively consisted of 60 white patients living in New England. Of these, 35 developed multiple sclerosis. Of the 35 only two were in the possible category, 12 were in the probable category, and 21 in the definite category. The most remarkable statistic is that 29 were women and only six were men. The mean follow-up was 14.9 years, and by use of a life-table analysis the authors were able to show that 74% of the women and 34% of the men will develop multiple sclerosis 15 years after an attack of optic neuritis. (2 figures, 4 tables, 28 references)—David Shoch

New England Journal of Medicine

Progression of diabetic retinopathy after pancreas transplantation for insulin-dependent diabetes mellitus. Ramsay, R. C., Goetz, F. C.,

Sutherland, D. E. R., Mauer, S. M., Robison, L. L., Cantrill, H. L., Knobloch, W. H., and Najarian, J. S. (Dept. Ophthalmol., Univ. Minnesota, Box 493, UMHC, 516 Delaware St. S.E., Minneapolis, MN 55455). N. Engl. J. Med. 318:208, 1988.

A group of 38 patients with advanced proliferative retinopathy were subjected to pancreas transplantation. In 22 of these patients, transplantation was successful; in 16 it was unsuccessful. Patients in the unsuccessful group acted as controls in the study of the progression of diabetic retinopathy. After two years there was no significant difference in the rate of progression of retinopathy. Success of the transplantation did not prevent progression. There was also no difference in the loss of vision between the two groups. Pancreas transplantation and resulting normal glycemia neither reverse nor prevent the progression of diabetic retinopathy. (5 figures, 1 table, 31 references)—David Shoch

Are continuing studies of metabolic control and microvascular complications in insulin-dependent diabetes mellitus justified? The Diabetes Control and Complications Trial Research Group. (The D.C.C.T. Res. Group, Bethesda, MD 20892). N. Engl. J. Med. 318:246, 1988.

Numerous studies have indicated that careful control of diabetes with use of insulin pumps or frequent insulin injections does not result in the reduction or delay the progression of retinopathy. However, none of these studies have been done in a truly prospective fashion with a randomization of patients to a control group and an experimental group. Further, no one has examined the possibility that careful control before the onset of retinopathy may prevent ocular problems from developing. In order to answer this question and to study the patients who already have retinopathy more carefully, a diabetes control and complications trial has been developed by the National Institute of Diabetes and Digestive and Kidney Diseases. The study, in progress for about five years, has enrolled 1,050 patients out of a planned enrollment of 1,400. The standard group receives one or two insulin injections per day while the experimental group follows a regimen of continuous subcutaneous infusion with insulin pumps or multiple daily injections and frequent self-monitoring of blood glucose. With 700 subjects in the primary-prevention group and 700 subjects in the secondary intervention cohort, the study should be able to detect significant change in the rate of the onset and progression of diabetic retinopathy. (1 table, 26 references)—David Shoch

Ophthalmologica

Effect of changing medication regimens in glaucoma patients. Novack, G. D., David, R., Lee, P. F., Freeman, M. I, Duzman, E., and Batoosingh, A. L. (Allergan Pharmaceuticals Inc., 2525 Dupont Dr., Irvine, CA 92715). Ophthalmologica 196:23, 1988.

When glaucoma medication fails to adequately control intraocular pressure, a second medication is frequently added. Before adding a second drug to patients whose intraocular pressure was no longer controlled by 0.5% timolol, the authors tested the effect of switching to another beta blocker, levobunolol (0.5 or 1%). The authors evaluated the effect of study participation on compliance in the control group continuing to receive 0.5% timolol. In each treatment group, the intraocular pressure of approximately 30-40% of the patients was successfully controlled for the 3-month study period. The remaining patients did not exhibit significant pressure reductions and were dropped from the study within two weeks. The authors concluded that (1) the results of 'switch' studies without a control group must be interpreted carefully, and (2) the initiation of a 'new regimen' with an equieffective beta blocker may be sufficient to increase compliance and thereby control intraocular pressure. (1 figure, 2 tables, 12 references)—Authors' abstract

Plastic and Reconstructive Surgery

Eyelid reconstruction in pachydermoperiostosis. Ohtsuka, M., and Takayanagi, S. (Div. Plast. Surg., Kokura Mem. Hosp., 1-1 Kifune-machi, Kokura-Kitaku, Kitakyushu 802, Japan). Plast. Reconstr. Surg. 81:88, 1988.

Pachydermoperiostosis is a syndrome of unknown origin in which the collagen bundles of skin are increased, the amount of mucopolysaccharides is also increased, and there is associated periosteosis. This rare disease frequently affects the eyelids, causing bogginess, thickening, and an inability to open the eyes. The upper eyelids tend to project over the lower eyelids and enlarge in a fan-shape. Acropathy of the fingers and toes is common. The authors describe the surgical procedure required to thin the eyelids in order to allow them to open. They chose to perform the procedure in two stages. First, a wedge excision of the tarsal-conjunctival layer allowed the eyelid to come into firm contact with the globe. Secondly, reduction of the upper tarsal plates and the conjunctiva was performed three weeks later. After these procedures the patient was able to open the eyes in a normal fashion. (6 figures, 4 references)—David Shoch

NEWS ITEMS

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The Journal invites information concerning meetings, postgraduate courses, lectures, honors, and appointments. Double space each item and provide the name and address of the responsible author. Announcements of courses, meetings, and lectures must be submitted at least six months before the date of the event.

Johns Hopkins Medical Institutions: First International Symposium on the Marfan Syndrome

The Johns Hopkins Medical Institutions will sponsor the First International Symposium on the Marfan Syndrome, July 8–10, 1988, in Baltimore, Maryland. For further information, write Program Coordinator, Office of Continuing Education, The Johns Hopkins Medical Institutions, Turner 22, 720 Rutland Ave., Baltimore, MD 21205.

Ninth International Congress of Eye Research

The Ninth International Congress of Eye Research will be held July 29–Aug. 4, 1990 in Helsinki, Finland. For further information, write Secretariat, Ninth International Congress of Eye Research, University of Helsinki, Department of Anatomy, Eye Research Laboratory, Siltavuorenpenger 20 A, SF-00170 Helsinki, Finland.

Canadian Implant Association: Fourteenth Annual Meeting

The Canadian Implant Association will hold its Fourteenth Annual Meeting, June 10 and 11, 1988, in Montreal, Canada. For further information, write Marvin L. Kwitko, Program Chairman, Canadian Implant Association, 5591 Cote des Neiges Rd., Suite #1, Montreal, Canada H3T 1Y8.

American Diopter and Decibel Society: Biennial Meeting

The American Diopter and Decibel Society will hold its biennial meeting, Jan. 21–28, 1989, in Acapulco, Mexico. For further information, write Jeannine L. Nee, Meeting Coordinator, American Diopter and Decibel Society, 3518 Fifth Ave., Pittsburgh, PA 15213.

American National Standards Institute: Revision of Standard for Prescription Ophthalmic Lenses

The American National Standards Institute has published a revised ANSI Z80.1-1987, Recommendations for Prescription Ophthalmic Lenses, to provide quality goals for new lenses prepared to individual prescription. The standard gives recommendations for refractive power, cylinder axis, prism power, segment location, thickness, impact resistance, spectrally attenuating materials, ultraviolet attenuating lenses, base curve, warpage, and physical quality and appearance. The appendix contains detailed test procedures to facilitate the standard's application.

Copies are available at $10.00 each from American National Standards Institute, Inc., 1430 Broadway, New York, NY 10018.

Albert Einstein College of Medicine/Montefiore Hospital: Fourteenth Annual Ophthalmology Symposium

Albert Einstein College of Medicine/Montefiore Hospital will sponsor the Fourteenth Annual Ophthalmology Symposium, June 3, 1988, in New York, New York. For further information, write Robert Saunders, Conference Planner, Einstein/Montefiore, Office of Continuing Medical Education, 3301 Bainbridge Ave., Bronx, NY 10467.

Henry Ford Hospital: Eleventh Annual Alumni Meeting

The Department of Ophthalmology of Henry Ford Hospital will hold its Eleventh Annual Alumni Meeting, June 3 and 4, 1988, in Detroit,

Michigan. For further information, write Leslie J. Fisher, Ph.D., Director, Ophthalmology Research Laboratory, Henry Ford Hospital, 2799 W. Grand Blvd., Detroit, MI 48202.

Johns Hopkins Medical Institutions: Eighteenth Anniversary Meeting of the Retinal Vascular Center Macula: A Potpourri

The Wilmer Institute of the Johns Hopkins Medical Institutions will sponsor the Eighteenth Anniversary Meeting of the Retinal Vascular Center of the Wilmer Institute entitled Macula: A Potpourri, July 15, 1988, in Baltimore, Maryland. For further information, write Program Coordinator, Office of Continuing Education, The Johns Hopkins Medical Institutions, Turner 22, 720 Rutland Ave., Baltimore, MD 21205.

Long Island Jewish Medical Center: A Clinical Day in Ophthalmology: Neuro-Ophthalmology

The Department of Ophthalmology of the Long Island Jewish Medical Center will sponsor a Clinical Day in Ophthalmology: Neuro-Ophthalmology, June 1, 1988, in New Hyde Park, New York. For further information, write Debra Mohr, Continuing Education Coordinator, Long Island Jewish Medical Center, New Hyde Park, NY 11042.

University of Maryland: Current Concepts in Ophthalmology: Eighth Annual Clinical Conference

The Department of Ophthalmology of the University of Maryland will sponsor Current Concepts in Ophthalmology: Eighth Annual Clinical Conference and the Second Annual Lois A. Young-Thomas Memorial Lecture, Sept. 23, 1988, in Baltimore, Maryland. For further information, write The Program of Continuing Education, University of Maryland School of Medicine, 10 S. Pine St., Suite 300, Baltimore, MD 21201.

State University of New York at Buffalo: Second Annual Resident and Alumni Conference

The State University of New York at Buffalo will hold its Second Annual Resident and Alumni Conference, June 3 and 4, 1988, in Buffalo, New York. For further information, write Elizabeth Rosiek, Administrator, Erie County Medical Center, 462 Grider St., Buffalo, NY 14215.

AKORN HEALS MARKET WOUNDS

THE AKORN STREET JOURNAL.

OL. LXXX NO. 11 ★★ National Edition FRIDAY JANUARY 1, 1988 Abita Springs, La. 50 CENT

Akorn Helps Doctors Recoup Losses

The smart money among the M.D.'s is moving to Akorn. It is no insider's secret that the quality line of Akorn ophthalmic products has produced more profits for less investment for ophthalmologists than any of Akorn's competitors. No minimum orders are required by Akorn and the company offers the best goods return policy available in the ophthalmic industry. The past year's sales reflect the interest shown by the profession.

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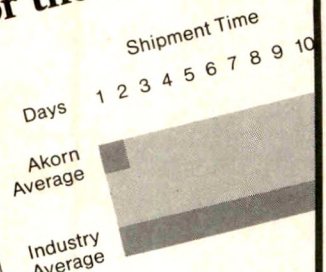
What's News

* * *

Looking forward to 1988, Akorn has again expanded its line of products. Making their debut in the Akorn line are solar shields, surgical drape supports, pen lights and lid scrub. These new additions to the Akorn line of ophthalmic products have increased the selection to over one hundred quality products. Each Akorn product meets the exacting standards that are required by the profession. The value provided by Akorn is present in all of the new product additions, dependable therapy, top quality and immediate delivery.

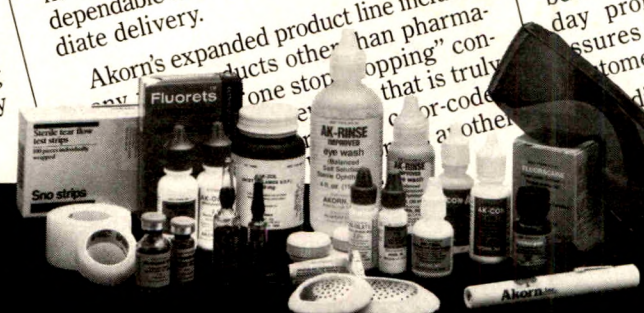
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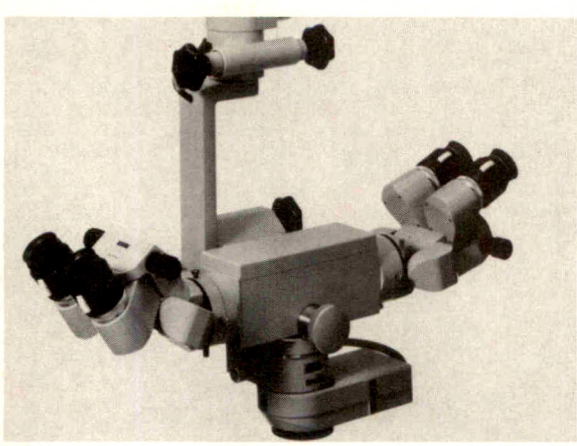
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Zeiss has introduced the OPMI MD Operation Microscope, featuring a short body, ergonomic design, and large 1:6 zoom range. It can be used as a single or double microscope. The instrument can be quickly and easily converted from one variant into another and combined with a wide range of accessories. Rotatable optics allow both traditional and face-to-face microsurgical procedures to be performed with the same microscope body. The double microscope is obtained by rotating the microscope body 90 degrees and mounting the stereo beam splitter.

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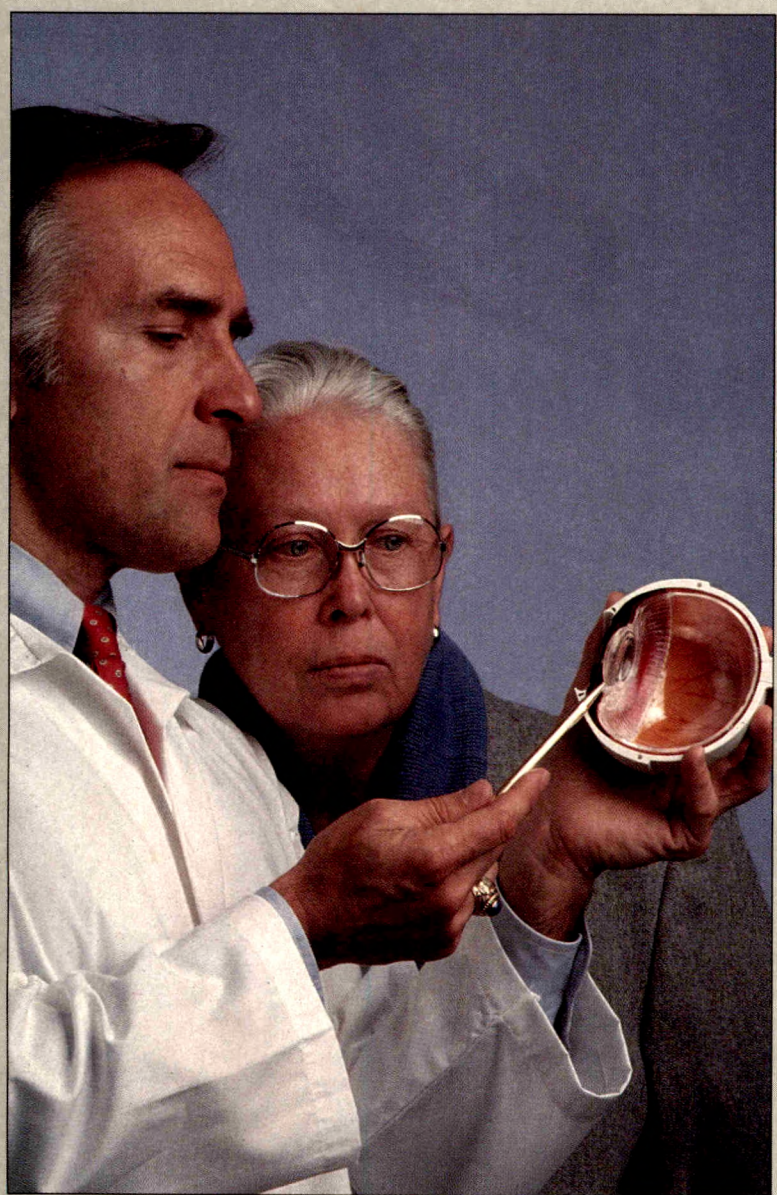
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CooperVision Ophthalmic Products, a unit of the Cooper Companies, has added to its Unisol line of preservative-free, pH balanced saline solutions by introducing aerosol packaging. Called Unisol Plus, the aerosol-packed saline is available in 8- and 12-oz cans. A special introductory 3-oz can is also available. Aerosol packaging is convenient for the consumer and provides safety and hygiene to the practitioner.

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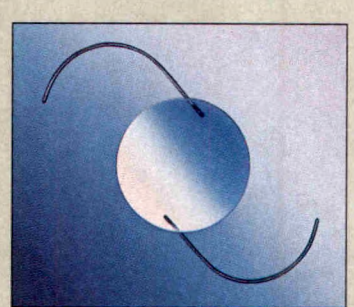
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Quality. You want high-quality products from a company that has an established reputation in health care. *With global health care sales over a billion dollars,* 3M is well-known for its high-quality, innovative products which result from a firm commitment to research and development.

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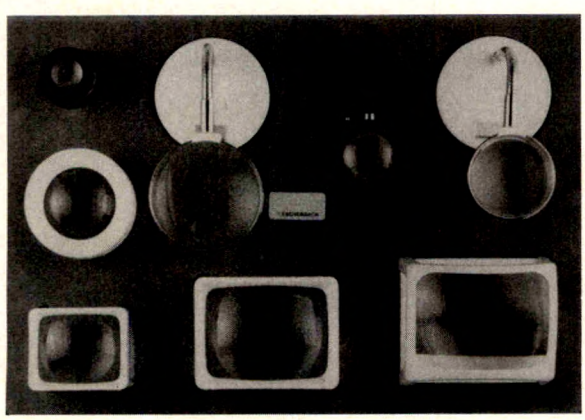
Low Vision Aids

Resources for Rehabilitation
33 Bedford St.
Suite 19-A
Lexington, MA 02173
Tel: (617) 862-6455

Resources for Rehabilitation announces publication of the "Living with Low Vision" series of patient education materials. This series of large-print resource lists has been designed for distribution by professionals to visually impaired individuals. Titles include "How to Keep Reading with Vision Loss," "Aging and Vision Loss," and "High Tech Aids," as well as disease-specific titles such as "Living with Diabetic Retinopathy," "Living with Glaucoma," and "Living with Macular Degeneration."

Resources for Rehabilitation has also produced the "Rehabilitation Resource Manual," a comprehensive desk reference for all professionals who serve visually impaired and blind individuals. The manual contains referral guidelines, lists referral resources by eye disease/condition and for special populations (youth, elders), and lists sources of assistive devices. Price: $20.00 (includes shipping and handling); standard print.

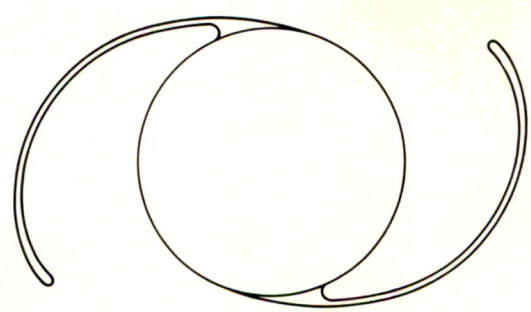
Eschenbach Optik of America, Inc.
25 November Trail
Weston, CT 06883
Tel: (203) 227-9409



Eschenbach Optik of America has introduced The Grand Stand, a new showcase collection of five transparent-base magnifiers and three gooseneck magnifiers. All eight stand magnifiers are designed to help visually impaired patients, senior citizens, and people in general in situations requiring hands-free magnification. The five transparent-base magnifiers range in power from ×3 to ×8. The transparent base eliminates shadows and provides good light, contrast, and visibility. The gooseneck magnifiers are constructed to make viewing easy, with or without spectacles. Price: $268.45.

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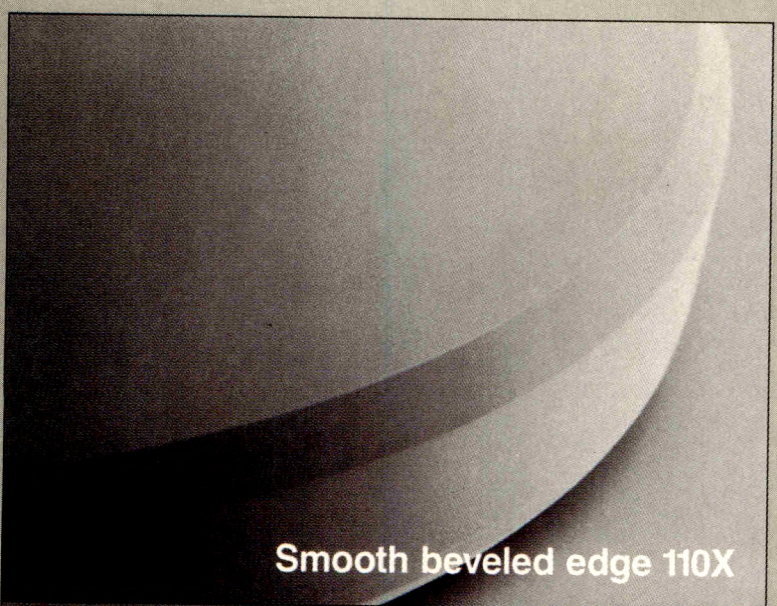


IOLAB has announced an addition to their Youens one-piece posterior chamber lens line with the introduction of Model 6840B, a 7-mm biconvex lens without positioning holes.

The Youens style IOLs are designed in cooperation with H. T. Youens, M.D., Houston, Texas. Each IOL is a one-piece, all PMMA, no-hole design with flexible Formflex II haptics. These lenses offer a large clear optical zone and haptics designed for ease of insertion and broad capsular contact.

Care

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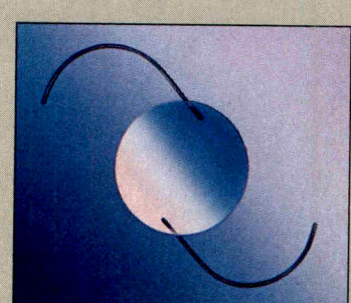
The rounded-tip haptics are tumble polished to minimize tissue trauma. Edges of the 6mm optic's extremely smooth surface are beveled to remove sharp edges. And the durable optic/haptic interface is precision engineered for a tight fit.

With the 15LE, you also get the proven performance of an all-PMMA lens with a UV-absorbent optic. The Easy-Flex™ haptics are designed for greater flexibility and easier insertion.

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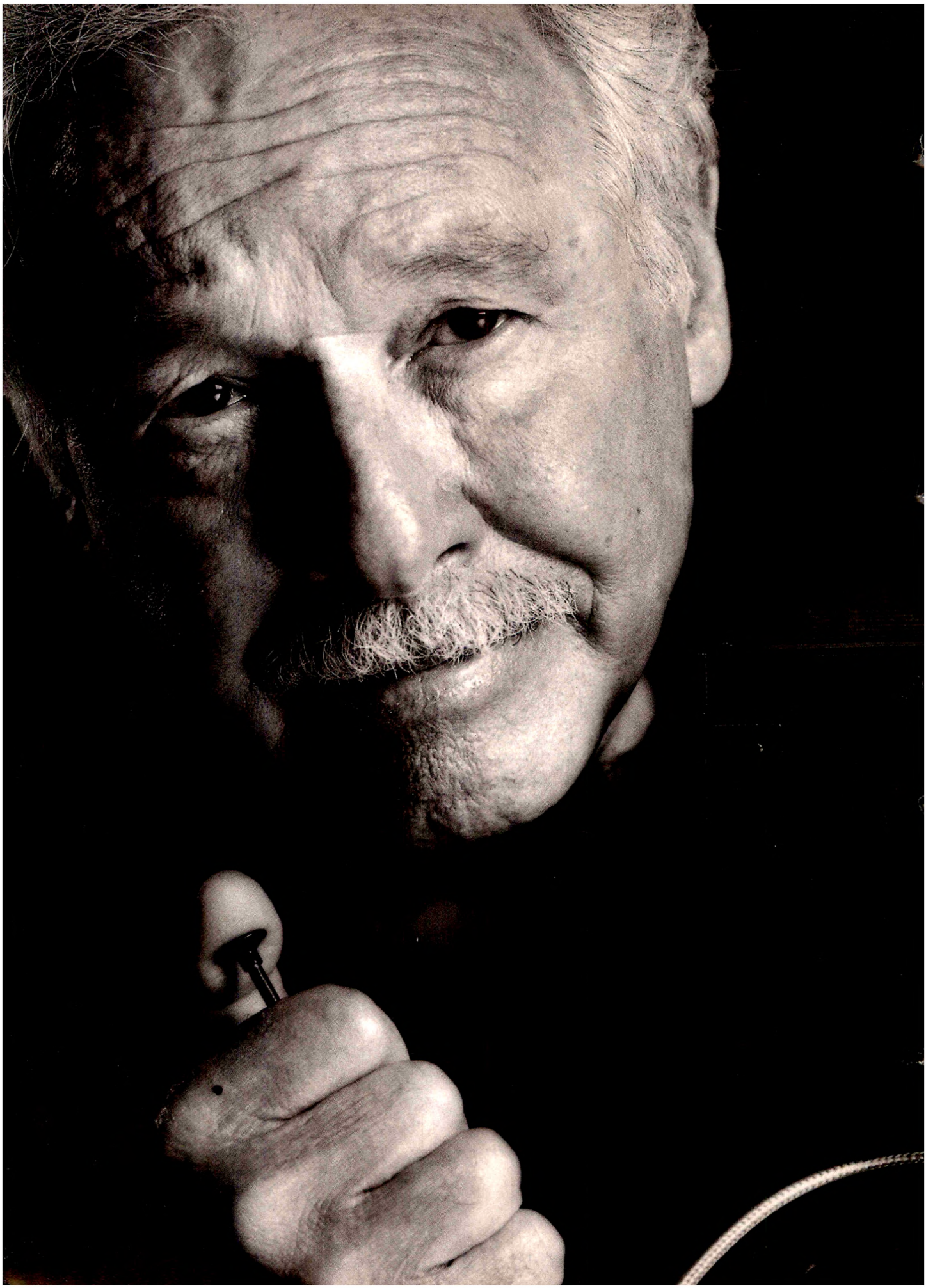


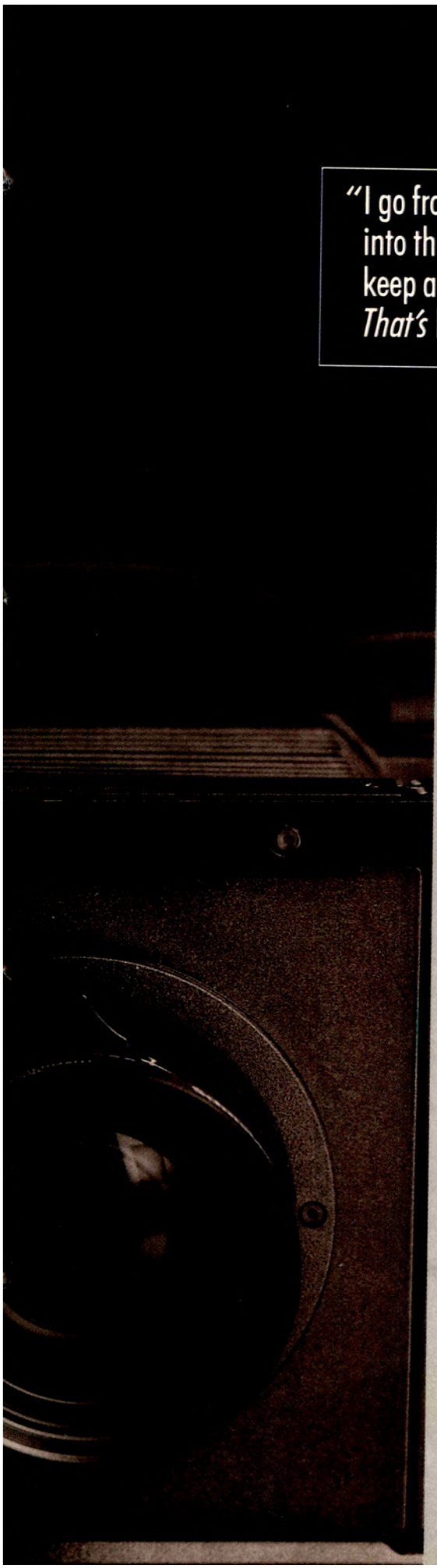
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Portrait of Noncompliance

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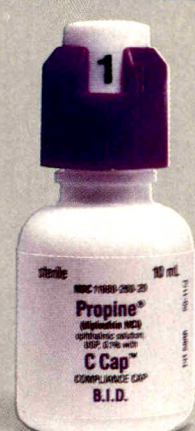
Propine with C Cap:

- Tracks next dose to be taken, and
- Minimizes confusion for patients on multidose therapy or multiple medications.

Propine with C Cap is available in 5 mL and 10 mL bottles. Propine is also available without C Cap.

Please see adjacent page for brief summary of prescribing information.

NEW C Cap™



Propine® (dipivefrin HCl)
sterile ophthalmic solution, USP, 0.1% with
C Cap™
Compliance Cap B.I.D.

Sig: Propine® with C Cap™

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ENCOURAGE COMPLIANCE. PROPINE® WITH C CAP™

Propine with C Cap encourages proper dosing by:

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- Minimizing confusion for patients on multidose therapy or multiple medications.

PROPINE® (dipivefrin HCl)
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INDICATIONS: Propine (dipivefrin HCl) is indicated as initial therapy for the control of intraocular pressure in chronic open-angle glaucoma. Patients responding inadequately to other antiglaucoma therapy may respond to addition of Propine. In controlled and open-label studies of glaucoma, Propine demonstrated a statistically significant intraocular pressure-lowering effect. Patients using Propine twice daily in studies with mean durations of 76-146 days experienced mean pressure reductions ranging from 20-24%. Therapeutic response to Propine twice daily is somewhat less than 2% epinephrine twice daily. Controlled studies showed statistically significant differences in lowering of intraocular pressure between Propine and 2% epinephrine. In controlled studies in patients with a history of epinephrine intolerance, only 3% of patients treated with Propine exhibited intolerance, while 55% of those treated with epinephrine again developed intolerance. Therapeutic response to Propine twice daily therapy is comparable to 2% pilocarpine 4 times daily. In controlled clinical studies comparing Propine and 2% pilocarpine, there were no statistically significant differences in the maintenance of IOP levels for the two medications. Propine does not produce miosis or accommodative spasm which cholinergic agents are known to produce. The blurred vision and night blindness often associated with miotic agents are not present with Propine therapy. Patients with cataracts avoid the inability to see around lenticular opacities caused by constricted pupil. **CONTRAINDICATIONS:** Propine® should not be used in patients with narrow angles since any dilation of the pupil may predispose the patient to an attack of angle-closure glaucoma. This product is contraindicated in patients who are hypersensitive to any of its components. **WARNING:** Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people. **PRECAUTIONS:** *Aphakic Patients.* Macular edema has been shown to occur in up to 30% of aphakic patients treated with epinephrine. Discontinuation of epinephrine generally results in reversal of the maculopathy. *Pregnancy: Pregnancy Category B.* Reproduction studies have been performed in rats and rabbits at daily oral doses up to 10 mg/kg body weight (5 mg/kg in teratogenicity studies), and have revealed no evidence of impaired fertility or harm to the fetus due to dipivefrin HCl. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. *Nursing Mothers.* It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Propine is administered to a nursing woman. *Usage in Children.* Clinical studies for safety and efficacy in children have not been done. *Animal Studies.* Rabbit studies indicated a dose-related incidence of meibomian gland retention cysts following topical administration of both dipivefrin hydrochloride and epinephrine. **ADVERSE REACTIONS:** *Cardiovascular Effects.* Tachycardia, arrhythmias and hypertension have been reported with ocular administration of epinephrine. *Local Effects.* The most frequent side effects reported with Propine alone were injection in 6.5% of patients and burning and stinging in 6%. Follicular conjunctivitis, mydriasis and allergic reactions to Propine have been reported infrequently. Epinephrine therapy can lead to adrenochrome deposits in the conjunctiva and cornea.

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Clinical Findings and Common Symptoms in Retinitis Pigmentosa

John R. Heckenlively, M.D., Seth L. Yoser, M.D., Lorraine H. Friedman, M.S., and Jill J. Oversier, B.S.

Data analysis was performed in a prospective study of clinical symptoms and findings in 500 patients with retinitis pigmentosa. The symptoms and findings in these patients met the usual definitions of the disease. At initial examination the patients were questioned in a standardized manner; symptoms and associated health problems were reviewed. Some patients were unable to answer all of the questions. Of the patients 274 (55%) were men and 226 (45%) were women, with a race distribution of 21 (4%) black, 47 (9%) Hispanic, 26 (5%) Oriental, three (1%) American Indian, and 403 (81%) white.

Sixty-nine patients reported no symptoms of night blindness and 116 patients claimed no visual field changes; 90 stated that they saw better at dusk. The most common problem noted by 263 (53.3%) was headaches, 31 on a daily basis, 42 at least weekly, 124 infrequently, and the remainder nonspecifically. Numbness or tingling, mainly in extremities, was reported by 99 patients. The second most common problem affecting 170 patients (34.6%) was light flashes; since eight patients had retinal detachments, light flashes cannot be totally discounted. Of 143 patients who had been pregnant, 14 had visual changes.

© American Journal of Ophthalmology 105:504–511, May, 1988

Corneal Infection in Mucosal Scarring Disorders and Sjögren's Syndrome

L. David Ormerod, M.D., Lye P. Fong, M.D., and C. Stephen Foster, M.D.

We reviewed 69 episodes of microbial keratitis occurring over an 11-year period in 56 patients with a mucosal scarring disorder or Sjögren's syndrome. Gram-positive bacterial isolates were the most common cause of infection, and accounted for almost all cases in patients with Sjögren's syndrome. Trichiasis (cicatricial pemphigoid), topical corticosteroids, bandage contact lenses, and corneal surgery were the main predisposing factors in the development of the corneal infection. In patients with ocular cicatricial pemphigoid, infection was much less common after chemotherapeutic control had been achieved. Recurrent infections were relatively frequent. There was a high rate of major complications, particularly in microbial keratitis complicating Sjögren's syndrome.

© American Journal of Ophthalmology 105:512–518, May, 1988

Presumed Autoimmune Corneal Endotheliopathy

Randal H. Paul, M.D.

I reviewed 20 previously published cases of presumed autoimmune corneal endotheliopathy. The disease appeared clinically with stromal edema and a slowly migrating line of keratic precipitates. All patients had acute stromal edema and keratic precipitates, and decreased visual acuity. Anterior chamber cells were noted in 11 patients. Inflammatory processes, such as pars planitis and iritis, and intraocular lens implantation were present in 13 patients.

© American Journal of Ophthalmology 105:519–522, May, 1988

Vitamin A Eyedrops for Superior Limbic Keratoconjunctivitis

Yuichi Ohashi, M.D., Hitoshi Watanabe, M.D., Shigeru Kinoshita, M.D., Hisashi Hosotani, M.D., Masayo Umemoto, M.D., and Reizo Manabe, M.D.

We treated 12 patients with superior limbic keratoconjunctivitis with topical vitamin A (retinol palmitate) eyedrops. After a follow-up period of at least three months, this therapy was found to be effective, to a varying extent, in ten patients (83%). Superior limbic keratoconjunctivitis lesions did not recur in these patients as long as topical application was continued.

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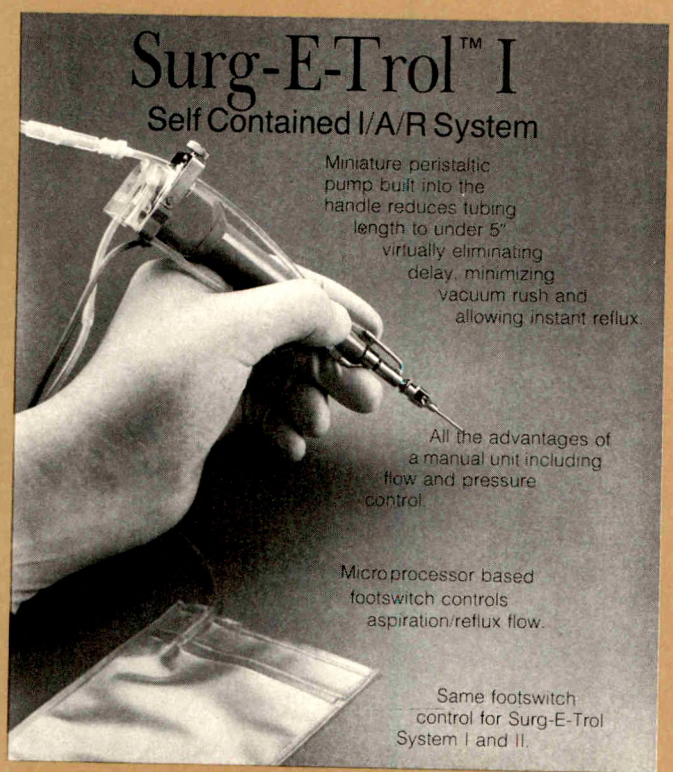
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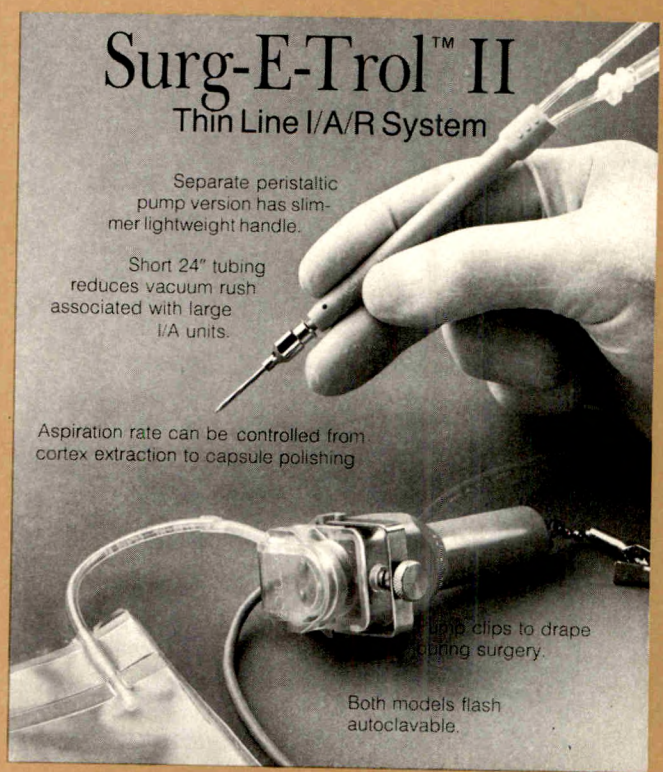
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An HLA-D Region Restriction Fragment Associated With Refractory Behçet's Disease

Jiro Numaga, M.D., Kazumasa Matsuki, M.D., Manabu Mochizuki, M.D., Mutsuhiko Minami, M.D., and Takeo Juji, M.D.

We examined the association between HLA-DQ and refractory Behçet's disease at the genomic DNA level. Using a restriction endonuclease *Taq* I and a DQβ cDNA probe, we identified the 1.9 kb DQβ restriction endonuclease fragment tightly associated with refractory Behçet's disease. This observation indicates that genomic HLA-DQ variations affect the development of refractory Behçet's disease.

© American Journal of Ophthalmology 105:528–533, May, 1988

Bilateral Anterior Uveitis and Interstitial Nephritis

James T. Rosenbaum, M.D.

Five patients had bilateral anterior uveitis associated with renal disease. Interstitial nephritis was histologically confirmed in three cases. Fatigue, anorexia, abdominal pain, weight loss, and anemia were common systemic complaints or findings. In each case, the uveitis was anterior, eventually bilateral, and associated with minimal visual impairment. Complications of the uveitis included increased intraocular pressure, synechiae, keratic precipitates, macular edema, and intraretinal hemorrhage as well as cells in the anterior vitreous humor and an exudate over the pars plana. Sjögren's syndrome, systemic lupus erythematosus, sarcoid, and syphilis were excluded as diagnoses that could explain the association of renal and uveal disease.

© American Journal of Ophthalmology 105:534–537, May, 1988

Quantitation of Tumor Seeding From Fine Needle Aspiration of Ocular Melanomas

Ben J. Glasgow, M.D., Harry H. Brown, M.D., Ana Maria Zargoza, M.D., and Robert Y. Foos, M.D.

Twenty-two fine needle (30 gauge) aspirations were performed in eyes enucleated for the clinical diagnosis of melanoma. Cytologic preparations were evaluated for adequacy of material, and needle tracts were evaluated for tumor implantation. A scleral marking method was used to identify all needle tracts. The number of tumor cells in tracts of direct transscleral aspirates was compared to those in tracts of indirect aspirates that traversed the anterior chamber or vitreous. Cellular material obtained with 30-gauge needles was sufficient for the diagnosis of malignant melanoma in all but one case. While 14 of 21 (67%) of all fine needle aspiration tracts and eight of 15 (53%) of indirect tracts contained tumor cells, the number of tumor cells was less than that associated with tumor growth in experimental models. Indirect aspirate tracts contained significantly fewer cells than tracts of direct aspirates ($P < .001$).

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Maternal Orbital Hematoma Associated With Labor

Daniel M. Jacobson, M.D., Kamel Itani, M.D., Kathleen B. Digre, M.D., Karl C. Ossoinig, M.D., and Michael W. Varner, M.D.

We examined two women with orbital hematomas that occurred during labor. Both women developed sudden diplopia, proptosis, and orbital pain. The location of the hematoma was confirmed by orbital echography and computed tomography. The patients were observed without surgical intervention. Neither patient developed clinical or echographic signs of compressive optic neuropathy. Clinical resolution occurred during the following two weeks. Serial standardized orbital echographic examinations documented resolution of the hematomas.

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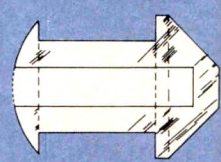
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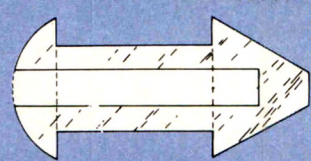
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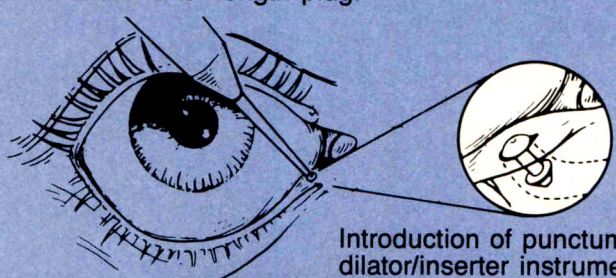
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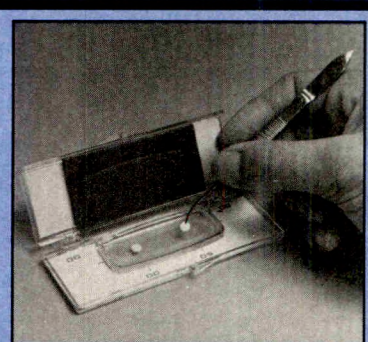
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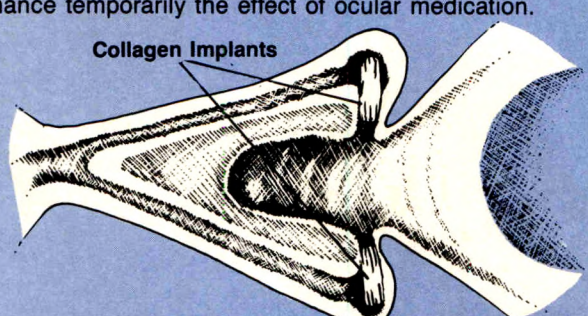
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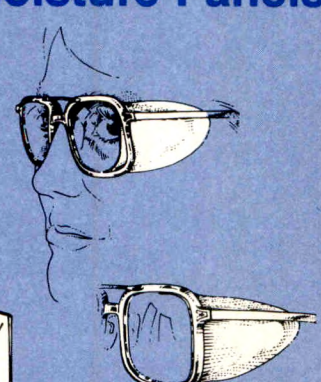
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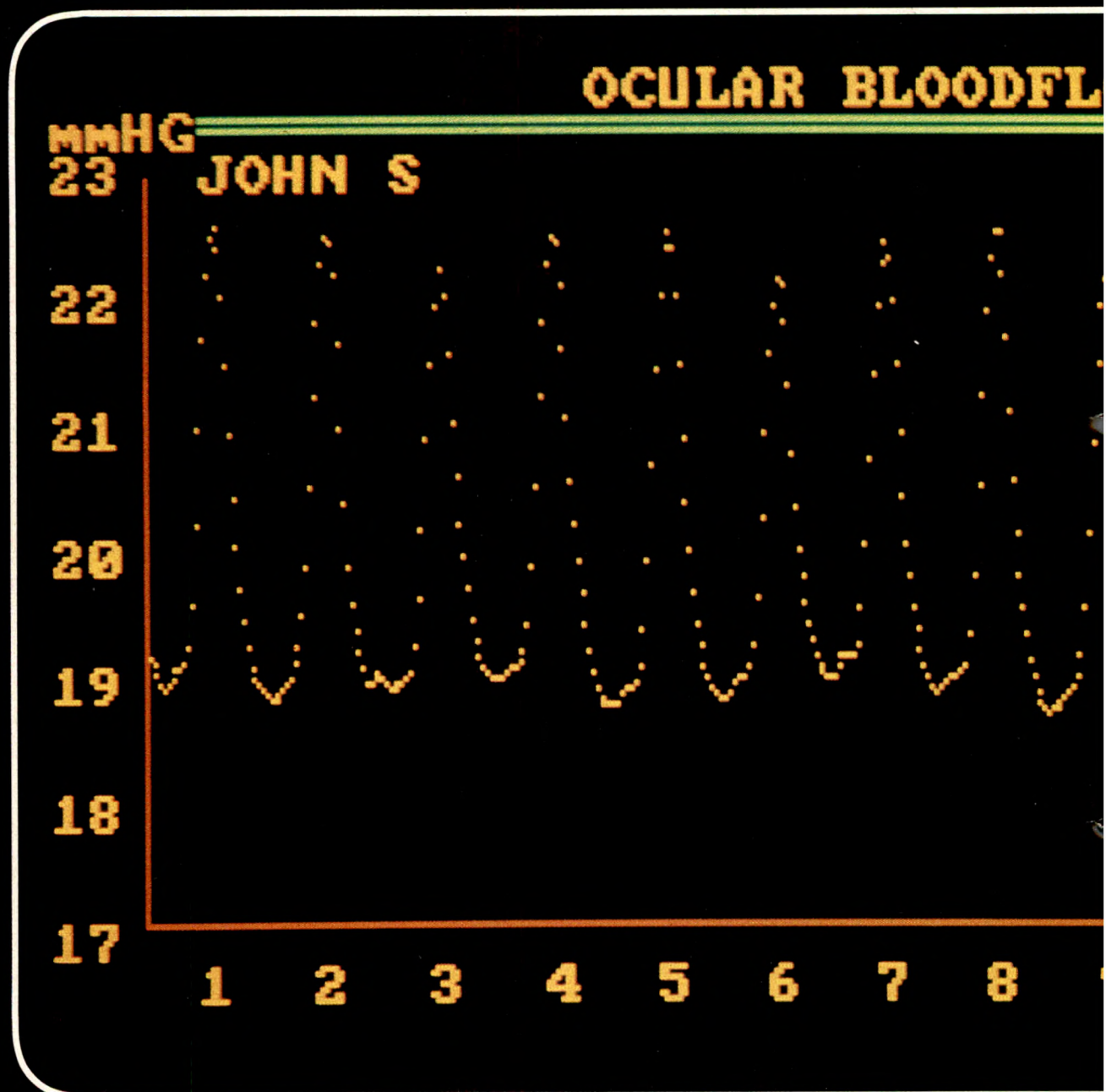
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3. Acute purulent infections of the eye may be masked or enhanced by the use of topical steroids.
4. Use of steroid medication in the presence of stromal herpes simplex requires caution and should be followed by frequent mandatory slit lamp microscopy.
5. As fungal infections of the cornea have been reported coincidentally with long-term local steroid applications, fungal invasion may be suspected in any persistent corneal ulceration where a steroid has been used, or is in use.
6. Use of topical corticosteroids may cause increased intraocular pressure in certain individuals. This may result in damage to the optic nerve with defects in the visual fields. It is advisable that the intraocular pressure be checked frequently.
7. **Use in Pregnancy**—Safety of intensive or protracted use of topical steroids during pregnancy has not been substantiated.

PRECAUTIONS
Posterior subcapsular cataract formation has been reported after heavy or protracted use of topical ophthalmic corticosteroids.

Patients with histories of herpes simplex keratitis should be treated with caution.

ADVERSE REACTIONS
Increased intraocular pressure, with optic nerve damage, defects in the visual fields. Also posterior subcapsular cataract formation, secondary ocular infections from fungi or viruses liberated from ocular tissues, and perforation of the globe when used in conditions where there is thinning of the cornea or sclera. Systemic side effects may occur with extensive use of steroids.

DOSAGE AND ADMINISTRATION
1 to 2 drops instilled into the conjunctival sac two to four times daily. During the initial 24 to 48 hours the dosage may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely.

NOTE: Keep this and all medications out of the reach of children.

HOW SUPPLIED
As a sterile suspension in 1 mL, 5 mL, 10 mL and 15 mL plastic dropper bottles. On prescription only.

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MEETINGS

"UPDATE ON RETINA-RELATED DISEASES AND SURGERY: CLINICALLY ORIENTED PROBLEMS AND SOLUTIONS": Cincinnati, Ohio. Contact: Educationl Services Department, The Christ Hospital, 2139 Auburn Avenue, Cincinnati, OH 45219, 513-369-2300.

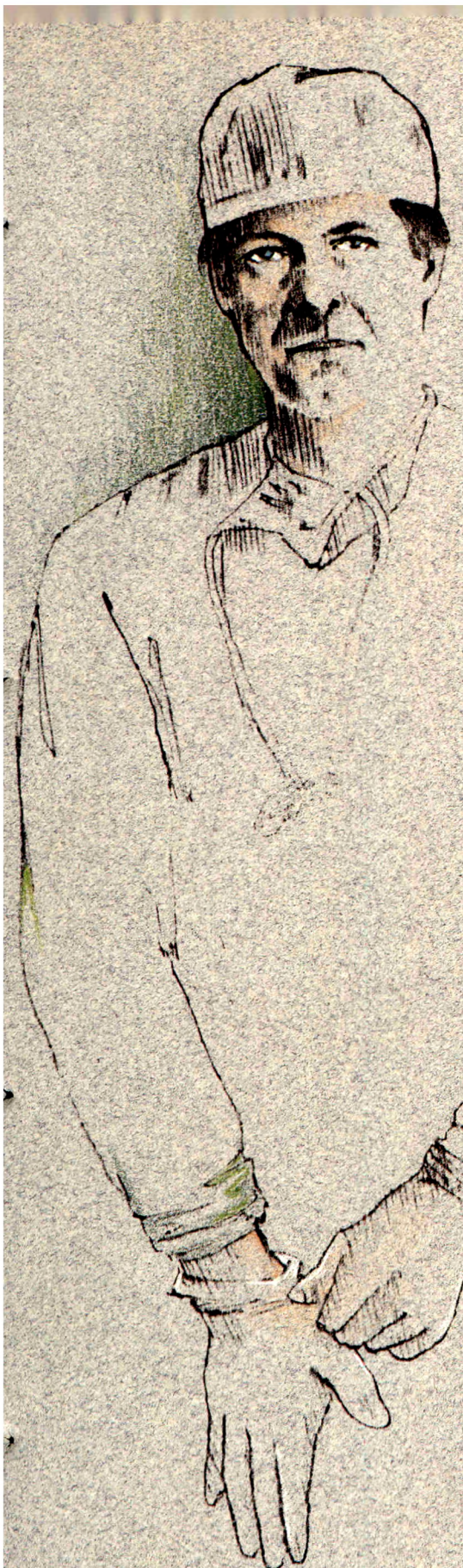
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Robt Maynor M.D.

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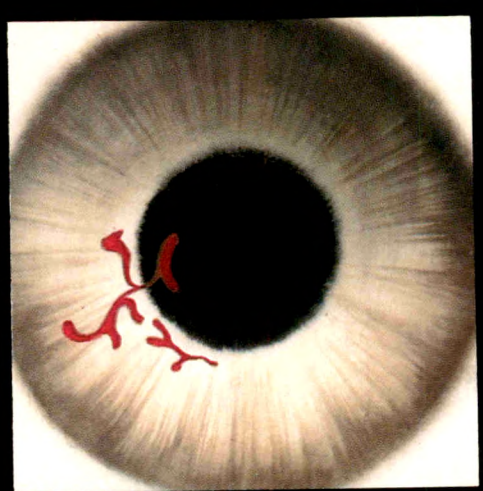
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More Effective for treating Dendritic Lesions

In two different clinical trials comparing Viroptic to IDU (idoxuridine) and ARA-A (adenine arabinoside or vidarabine) in the healing of dendritic lesions, Viroptic demonstrated superior efficacy.[1,2]



(Medical artist's conception of typical Dendritic Lesion)

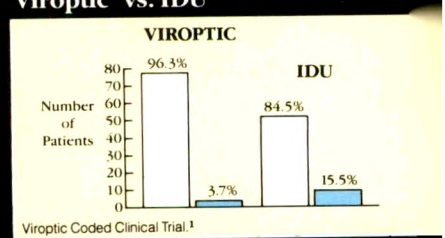
More Effective for treating Geographic Lesions

In two different clinical trials comparing Viroptic to IDU and ARA-A in the healing of geographic lesions, Viroptic again proved to be superior in efficacy.[1,2]



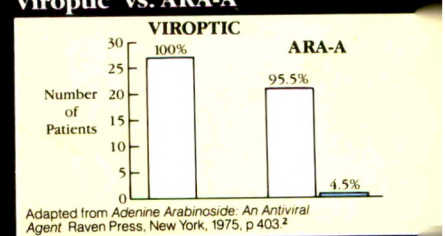
(Medical artist's conception of typical Geographic Lesion)

Viroptic® vs. IDU



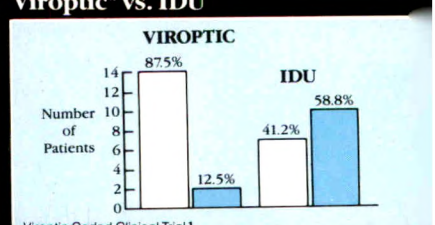
Viroptic Coded Clinical Trial.[1]

Viroptic® vs. ARA-A



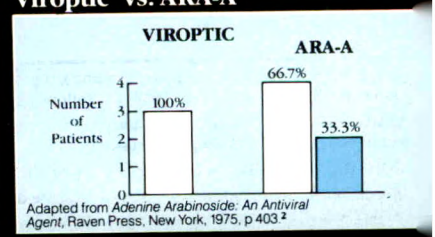
Adapted from *Adenine Arabinoside: An Antiviral Agent* Raven Press, New York, 1975, p 403.[2]

Viroptic® vs. IDU



Viroptic Coded Clinical Trial.[1]

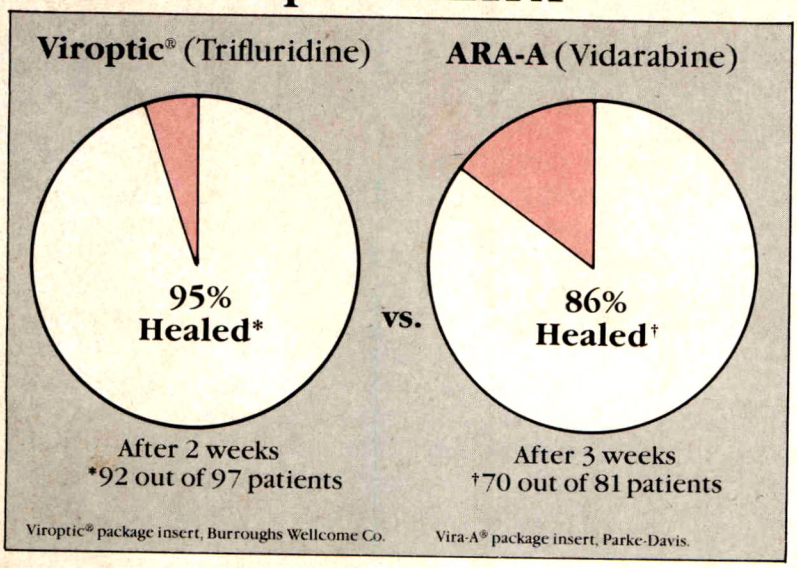
Viroptic® vs. ARA-A



Adapted from *Adenine Arabinoside: An Antiviral Agent*, Raven Press, New York, 1975, p 403.[2]

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Viroptic® vs ARA-A



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"We do use idoxuridine and vidarabine where acute infections do not respond to trifluridine, but, in my opinion, trifluridine is now the drug of choice for the treatment of superficial herpes, with no exceptions."[3]

References

1. Data on file, Medical Division, Burroughs Wellcome Co.
2. McKinnon JR, McGill JI, Jones BR: A coded clinical evaluation of adenine arabinoside and trifluorothymidine in the treatment of ulcerative herpetic keratitis, in Pavan-Langston D, Buchanan RA, Alford CA Jr (eds): *Adenine Arabinoside: An Antiviral Agent*, Raven Press, New York, 1975, p 403.
3. Kaufman HE, Centifanto-Fitzgerald YM, Varnell ED: Herpes simplex keratitis. *Ophthalmology* 1983;90:700-706.

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CONTRAINDICATIONS: Hypersensitivity or chemical intolerance to trifluridine.

WARNINGS: Do not administer more than nine drops daily. If there is no sign of improvement after seven days or complete re-epithelialization has not occurred after 14 days, other forms of therapy should be considered. Avoid administering VIROPTIC continuously for longer than 21 days.

PRECAUTIONS:

General: Prescribe only for clinically diagnosed herpetic keratitis. May cause mild local irritation (usually transient). Viral resistance may possibly develop, though it has not been reported *in vitro*.

Drug Interactions: VIROPTIC has been administered without apparent adverse interaction with certain antibiotics, certain steroids, and certain other ophthalmic drugs. Please see complete prescribing information.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies of mutagenicity and oncogenicity have been inconclusive.

Pregnancy: Do not use in pregnant women unless potential benefits outweigh potential risks. Based upon animal findings, it is unlikely that VIROPTIC would cause embryonic or fetal damage if given in recommended ophthalmic dosage to pregnant women. A safe dose has not been established for human embryo or fetus.

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ADVERSE REACTIONS: Most frequently reported: mild, transient burning or stinging upon instillation (4.6%), palpebral edema (2.8%). Others, in decreasing order of frequency: superficial punctate keratopathy, epithelial keratopathy, hypersensitivity reaction, stromal edema, irritation, keratitis sicca, hyperemia, increased intraocular pressure.

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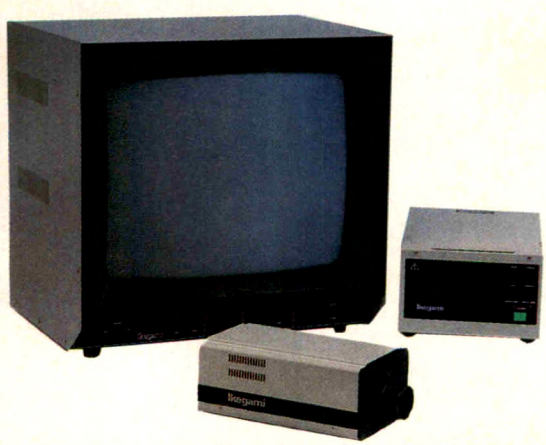
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The ITC-370M camera shown here in a typical research microscope configuration.

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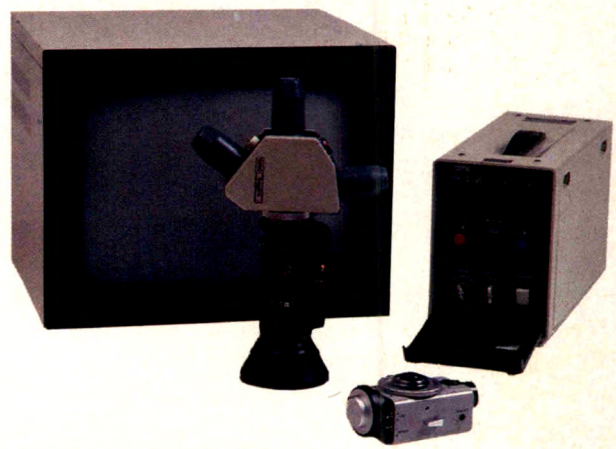
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Applications:

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Biomedical & Research: For documenting experimental data.

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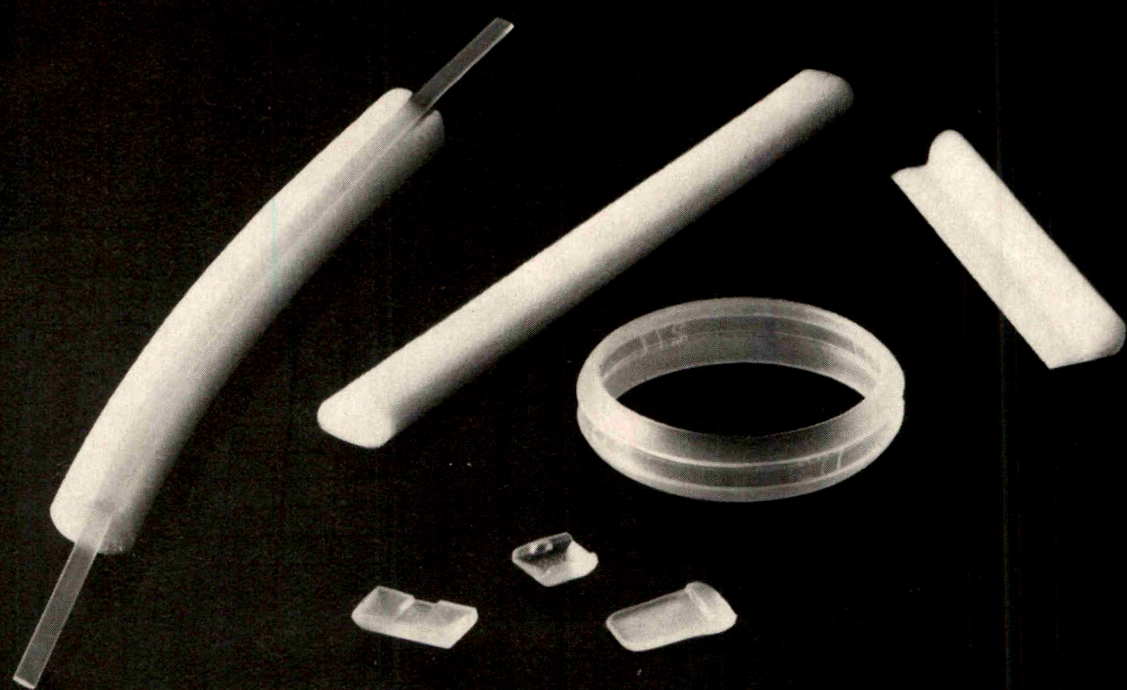
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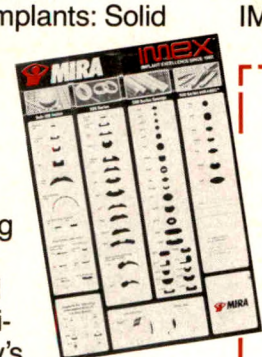
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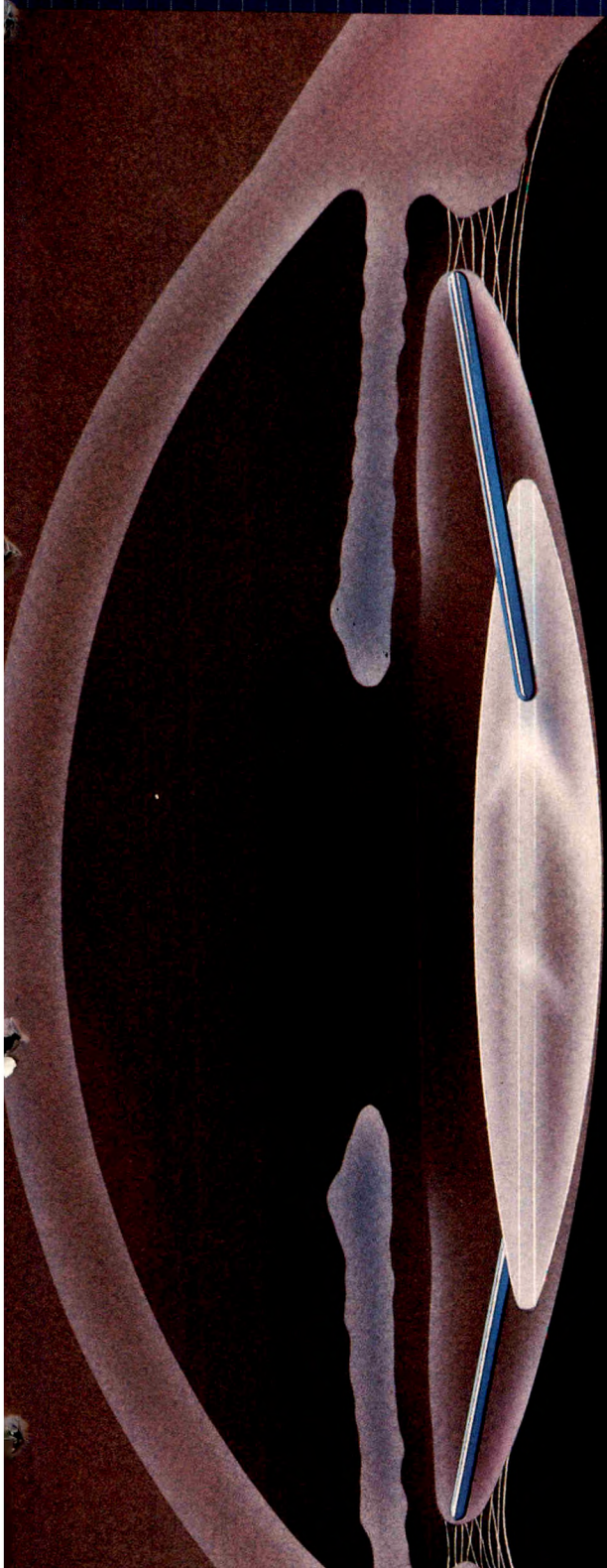
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*Mainster MA: The spectra, classification and rationale of ultraviolet-protective intraocular lenses. Am J Ophthalmol 1986; 102:727-732.

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Each gram of ointment contains: Tobramycin 0.3% (3 mg/g), Mineral Oil, White Petrolatum, and Chlorobutanol (0.5%) as a preservative. DM-00
Tobramycin is a water-soluble aminoglycoside antibiotic active against a wide variety of gram-negative and gram-positive ophthalmic pathogens.

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In Vitro Data: In vitro studies have demonstrated tobramycin is active against susceptible strains of the following microorganisms:
Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.
Streptococci, including some of the Group A–betahemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae*.
Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis (indole-negative) and indole-positive. *Proteus* species, *Haemophilus influenzae* and *H. aegyptius, Moraxella lacunata,* and *Acinetobacter calcoaceticus (Herellea vaginacola)* and some *Neisseria* species. Bacterial susceptibility studies demonstrate that in some cases, microorganisms resistant to gentamicin retain susceptibility to tobramycin. A significant bacterial population resistant to tobramycin has not yet emerged; however, bacterial resistance may develop upon prolonged use.

INDICATIONS AND USAGE: TOBREX is a topical antibiotic indicated in the treatment of external infections of the eye and its adnexa caused by susceptible bacteria. Appropriate monitoring of bacterial response to topical antibiotic therapy should accompany the use of TOBREX. Clinical studies have shown tobramycin to be safe and effective for use in children.

CONTRAINDICATIONS: TOBREX Ophthalmic Solution and Ointment are contraindicated in patients with known hypersensitivity to any of their components.

WARNINGS: NOT FOR INJECTION INTO THE EYE. Sensitivity to topically applied aminoglycosides may occur in some patients. If a sensitivity reaction to TOBREX® occurs, discontinue use.

PRECAUTIONS: As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. Ophthalmic ointments may retard corneal wound healing.
Pregnancy Category B. Reproduction studies in three types of animals at doses up to thirty-three times the normal human systemic dose have revealed no evidence of impaired fertility or harm to the fetus due to tobramycin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers: Because of the potential for adverse reactions in nursing infants from TOBREX, a decision should be made whether to discontinue nursing the infant or discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS: The most frequent adverse reactions to TOBREX Ophthalmic Solution and Ointment are localized ocular toxicity and hypersensitivity, including lid itching and swelling, and conjunctival erythema. These reactions occur in less than three of 100 patients treated with TOBREX. Similar reactions may occur with the topical use of other aminoglycoside antibiotics. Other adverse reactions have not been reported from TOBREX therapy; however, if topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration.
In clinical trials, TOBREX Ophthalmic Ointment produced significantly fewer adverse reactions (3.7%) than did Garamycin Ophthalmic Ointment (10.6%).

OVERDOSAGE: Clinically apparent signs and symptoms of an overdose of TOBREX Ophthalmic Solution or Ointment (punctate keratitis, erythema, increased lacrimation, edema and lid itching) may be similar to adverse reaction effects seen in some patients.

DOSAGE AND ADMINISTRATION: *SOLUTION:* In mild to moderate disease, instill one or two drops into the affected eye(s) every four hours. In severe infections, instill two drops into the eye(s) hourly until improvement, following which treatment should be reduced prior to discontinuation.
OINTMENT: In mild to moderate disease, apply a half-inch ribbon into the affected eye(s) two or three times per day. In severe infections, instill a half-inch ribbon into the affected eye(s) every three to four hours until improvement, following which treatment should be reduced prior to discontinuation.
How to Apply TOBREX® Ointment
1. Tilt your head back.
2. Place a finger on your cheek just under your eye and gently pull down until a "V" pocket is formed between your eyeball and your lower lid.
3. Place a small amount (about ½ inch) of TOBREX in the "V" pocket. Do not let the tip of the tube touch your eye.
4. Look downward before closing your eye.

TOBREX Ointment may be used in conjunction with TOBREX Solution.

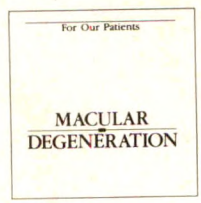
HOW SUPPLIED: STERILE solution in 5 ml Drop-Tainer® dispenser (NDC 0998-0643-05), containing tobramycin 0.3% (3 mg/ml) and STERILE ointment in 3.5 g ophthalmic tube (NDC 0065-0644-35), containing tobramycin 0.3% (3 mg/g).
STORAGE: Store at 8°-27°C (46°-80°F).
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References:

1. Bac-Data Bacteriologic Reports, Bac-Data Medical Information Systems Inc.
2. Data on file, Alcon Laboratories, Inc.

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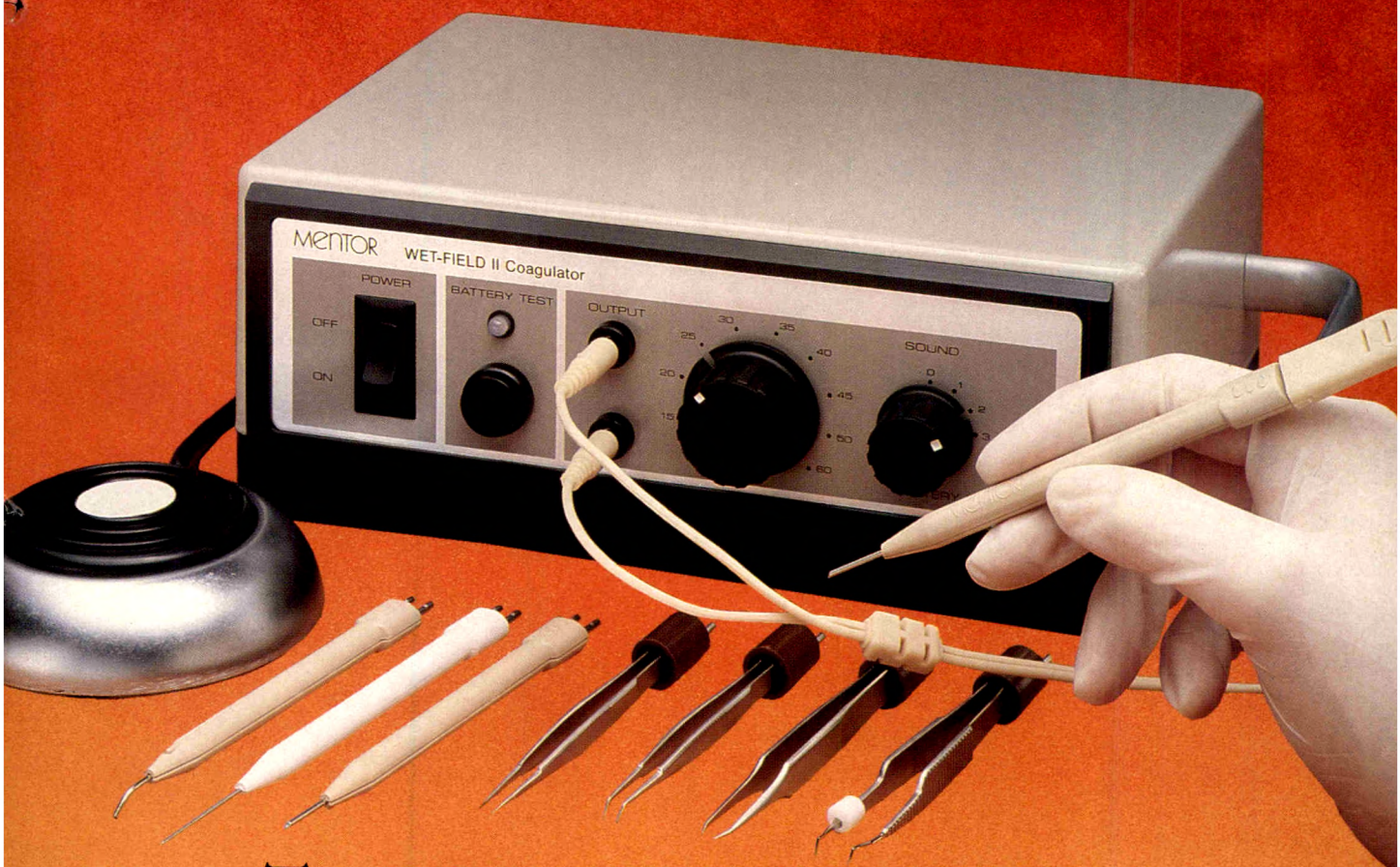
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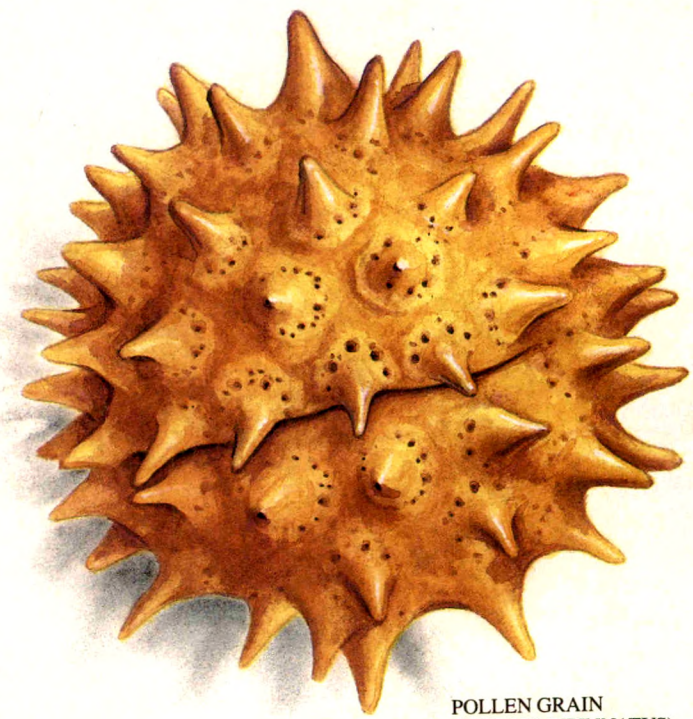
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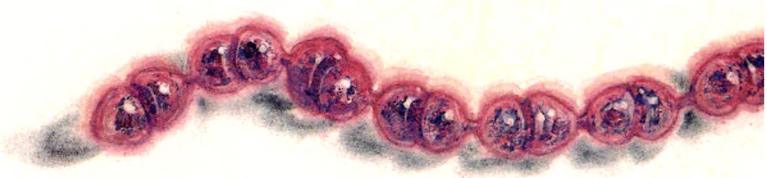
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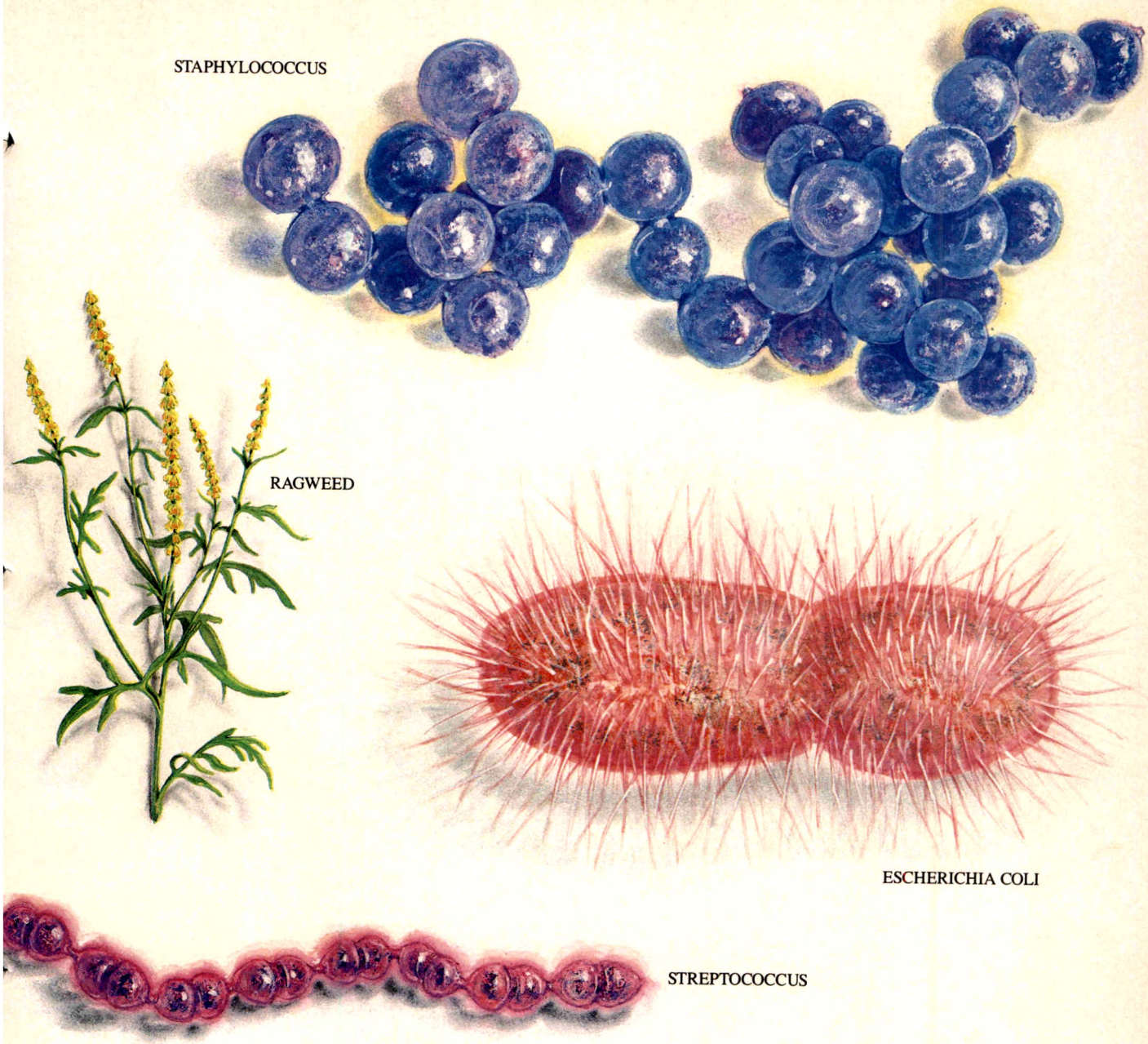
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[1]Reference: Allergan Pharmaceuticals Report Series, No. 188, 1982. The clinical significance of these animal data is unknown.

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PRECAUTIONS: Sulfacetamide preparations are incompatible with silver preparations.

Nonsusceptible organisms, including fungi, may proliferate with the use of this preparation. Sulfonamides are inactivated by the aminobenzoic acid present in purulent exudates. Sensitization may occur when a sulfonamide is re-administered irrespective of the route of administration, and cross-sensitivity between different sulfonamides may occur. If signs of sensitivity or other untoward reactions occur, discontinue use of the preparation.

ADVERSE REACTIONS: Sulfacetamide sodium may cause local irritation, stinging and burning. While the irritation may be transient, occasionally, use of the medication has to be discontinued.

Although sensitivity reactions to sulfacetamide sodium are rare, an isolated incident of Stevens-Johnson syndrome was reported in a patient who had experienced a previous bullous drug reaction to an orally administered sulfonamide, and a single instance of local hypersensitivity was reported which progressed to a fatal syndrome resembling systemic lupus erythematosus.

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(sulfacetamide sodium - prednisolone acetate)
Liquifilm® sterile ophthalmic suspension

INDICATIONS AND USAGE: A steroid/anti-infective combination is indicated for steroid- responsive inflammatory ocular conditions for which a corticosteroid is indicated and where bacterial infection or a risk of bacterial ocular infection exists.

Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe where the inherent risk of steroid use in certain infective conjunctivitides is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

The particular anti-infective drug in this product is active against the following common bacterial eye pathogens: *Escherichia coli, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus (viridans group), Pseudomonas* species, *Haemophilus influenzae, Klebsiella* species, and *Enterobacter* species. This product does not provide adequate coverage against *Neisseria* species and *Serratia marcescens.*

CONTRAINDICATIONS: Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, and many other viral diseases of the cornea and conjunctiva. Mycobacterial infection of the eye. Fungal diseases of the ocular structures. Hypersensitivity to a component of the medication. (Hypersensitivity to the antimicrobial component occurs at a higher rate than for other components.)

The use of these combinations is always contraindicated after uncomplicated removal of a corneal foreign body.

WARNINGS: Prolonged use may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Prolonged use may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection. If these products are used for 10 days or longer, intraocular pressure should be routinely monitored even though it may be difficult in children and uncooperative patients.

Employment of a steroid medication in the treatment of herpes simplex requires great caution.

A significant percentage of staphylococcal isolates are completely resistant to sulfa drugs.

PRECAUTIONS: The initial prescription and renewal of the medication order beyond 20 milliliters should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

The possibility of fungal infections of the cornea should be considered after prolonged steroid dosing.

ADVERSE REACTIONS: Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component, or the combination. Exact incidence figures are not available since no denominator of treated patients is available.

Reactions occurring most often from the presence of the anti-infective ingredient are allergic sensitizations. The reactions due to the steroid component in decreasing order of frequency are: elevation of intraocular pressure (IOP) with possible development of glaucoma, and infrequent optic nerve damage; posterior subcapsular cataract formation; and delayed would healing.

Secondary infection: The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroid. The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used.

Secondary bacterial ocular infection following suppression of host responses also occurs.

FML®

(fluorometholone) 0.1%
Liquifilm® sterile ophthalmic suspension

INDICATIONS AND USAGE: FML is indicated for the treatment of corticosteroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe.

CONTRAINDICATIONS: FML is contraindicated in the following conditions:

Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, and other viral diseases of the cornea and conjunctiva.

Tuberculosis of the eye.

Fungal diseases of the ocular structures.

Hypersensitivity to any component of the medication.

WARNINGS: Corticosteroid medication in the treatment of patients with a history of herpes simplex keratitis (involving the stroma) requires great caution; frequent slit lamp microscopy is mandatory.

Prolonged use may result in elevation of IOP, with damage to the optic nerve, defects in visual acuity and fields of vision, and/or in posterior subcapsular cataract formation. It may also aid in the establishment of secondary ocular infections from fungi or viruses liberated from ocular tissues.

Various ocular diseases and long-term use of topical corticosteroids have been known to cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation.

Acute purulent untreated infection of the eye may be masked or activity enhanced by the presence of corticosteroid medication.

PRECAUTIONS: General: As fungal infections of the cornea are particularly prone to develop coincidentally with long-term local corticosteroid applications, fungal invasion must be suspected in any persistent corneal ulceration where a corticosteroid has been used or is in use.

Intraocular pressure should be checked frequently.

Carcinogenesis, mutagenesis, impairment of fertility: No studies have been conducted in animals or in humans to evaluate the possibility of these effects with fluorometholone.

Pregnancy Category C: Fluorometholone has been shown to be teratogenic and embryocidal in rabbits when given in doses approximating the human dose and above. There are no adequate, well-controlled studies in pregnant women. Fluorometholone should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Fluorometholone was ocularly applied to both eyes of pregnant rabbits at various dosage levels on days 6 to 18 of gestation. A significant dose-related increase in fetal abnormalities and in fetal loss was observed.

Nursing Mothers: It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk, nevertheless, the physician should consider the patient discontinuing nursing while the drug is being administered.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Adverse reactions include, in decreasing order of frequency, elevation of intraocular pressure (IOP) with possible development of optic nerve damage; loss of visual acuity or defects in fields of vision; posterior subcapsular cataract formation; delayed wound healing.

The following have also been reported after the use of topical corticosteroids: Secondary ocular infection from pathogens liberated from ocular tissues and, rarely, perforation of the globe when used in conditions where there is thinning of the cornea or sclera.

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A Proposed Mild Type of Acute Retinal Necrosis Syndrome

Toshihiko Matsuo, M.D., Tadashi Nakayama, M.D., Tetsuro Koyama, M.D., Masaya Koyama, M.D., and Nobuhiko Matsuo, M.D.

Six patients had peripheral to midperipheral pale yellow retinal exudates typical of acute retinal necrosis syndrome but which extended gradually to the posterior pole and remained isolated without becoming confluent. These exudates resulted in localized retinochoroidal degeneration without retinal detachment, in contrast to acute retinal necrosis syndrome. Antibody titers in aqueous humor were increased to varicella-zoster virus in some of the patients examined. The findings led us to hypothesize that this mild, self-limiting course is one of the natural developments of acute retinal necrosis syndrome, although somewhat modified by corticosteroid or acyclovir therapy, and that acute retinal necrosis syndrome consists of varying degrees of severity from mild to fulminant types.

© American Journal of Ophthalmology 105:579–583, June, 1988

Asymmetric Retinopathy in Patients With Diabetes Mellitus

David J. Browning, M.D., Harry W. Flynn, Jr., M.D., and George W. Blankenship, M.D.

We reviewed retrospectively the records of 57 diabetic patients with asymmetric retinopathy persisting for two years or more (mean, 4.8 years) to identify intraocular risk and protective factors for the development of proliferative retinopathy. For each patient in this series, the more severely affected eye had proliferative retinopathy and the fellow eye had either background diabetic retinopathy or no retinopathy. Branch vein occlusion ($P = .016$) was identified as a statistically significant risk factor for proliferative retinopathy and chorioretinal scarring ($P = .031$) was found to be a statistically significant protective intraocular factor. In 34 patients with long-standing asymmetric retinopathy, no intraocular risk or protective factors were identified.

© American Journal of Ophthalmology 105:584–589, June, 1988

Detection of the Carrier State of X-Linked Retinoschisis

Geoffry B. Arden, M.D., Michael B. Gorin, M.D., Philip J. Polkinghorne, M.D., Marcelle Jay, Ph.D., and Alan C. Bird, M.D.

We determined the extent of suppressive rod-cone interaction in 11 obligate carriers and eight potential carriers of X-linked retinoschisis from eight families. Despite otherwise normal ophthalmoscopic and functional testing, all of the obligate heterozygous carriers demonstrated a complete absence of normal rod-cone interaction. Of the potential heterozygous carriers, three had normal rod-cone interactions, two had no detectable interaction, and two yielded technically unsatisfactory results. This lack of rod-cone interactions allows heterozygous individuals to be identified clinically and has implications concerning the origin of this inherited disorder.

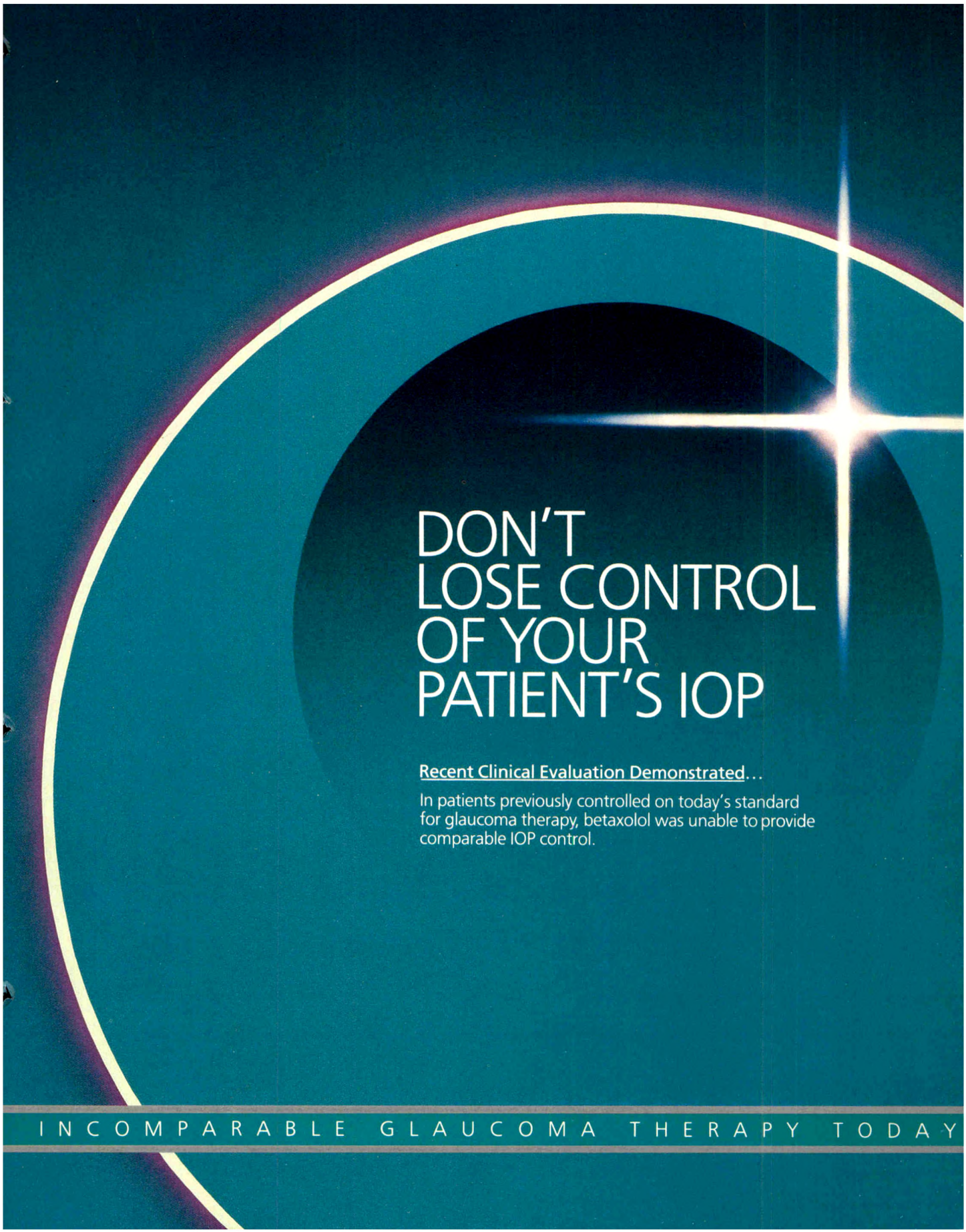
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Detection of Lymphocytes in the Vitreous Gel of Patients With Retinitis Pigmentosa

David A. Newsome, M.D., and Ronald G. Michels, M.D.

We used monoclonal antibodies against specific T cell, B cell, and macrophage antigens to detect immune system cells in the vitreous gel of retinitis pigmentosa patients. Vitreous samples were obtained by biopsy from three patients and by dissection from eight postmortem donor eyes. All samples contained CD4, T helper and CD8, suppressor cells, activated T cells, some B cells, and macrophages. About one third of the cells were nonreactive. Vitreous gel from normal controls contained mostly nonreactive cells with a few macrophages and rare T cells. These observations further indicated the nature of the cellular reaction in retinitis pigmentosa and characterized the biomicroscopically visible particulate bodies characteristically seen in the vitreous gel of these patients.

© American Journal of Ophthalmology 105:596–602, June, 1988

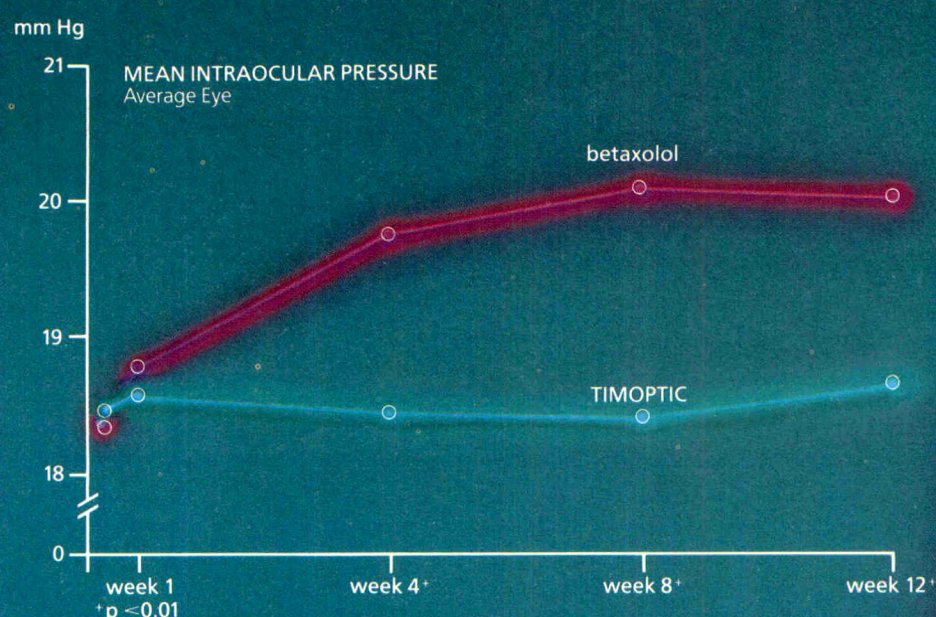

DON'T
LOSE CONTROL
OF YOUR
PATIENT'S IOP
Recent Clinical Evaluation Demonstrated...
In patients previously controlled on today's standard for glaucoma therapy, betaxolol was unable to provide comparable IOP control.
INCOMPARABLE GLAUCOMA THERAPY TODAY

DON'T LOSE CONTROL OF YOUR PATIENT'S IOP

In a multicenter study, recent clinical evaluation,[1,2] of 353 patients with a history of satisfactory IOP control and tolerability while on TIMOPTIC® (Timolol Maleate, MSD):

- Confirmed the benefits of maintaining therapy with TIMOPTIC for IOP control
- Demonstrated that TIMOPTIC surpassed Betoptic in maintaining IOP control

In patients previously controlled on TIMOPTIC, Betoptic was unable to maintain comparable IOP control:



At week 12, 97% of 149 patients on TIMOPTIC continued to be satisfactorily controlled.

At weeks 4, 8, and 12, significant increases in baseline IOP ($p \leq 0.01$) were seen in the patients treated with Betoptic.

[1]Data available upon request from Merck Sharp & Dohme, Professional Services Department, West Point, PA 19486.

[2]A total of 353 patients whose IOP was satisfactorily controlled with TIMOPTIC and in whom the drug was well tolerated were continued on TIMOPTIC 0.5% b.i.d. during a 2-week baseline period. Patients contributing data were then randomly assigned in a double-masked fashion in demographically similar groups to continue to receive either TIMOPTIC 0.5% b.i.d. (n = 149) or Betoptic 0.5% b.i.d. (n = 146). Following a baseline measurement, patients were evaluated for IOP after 1, 4, 8, and 12 weeks of therapy. In the average-eye approach, values from the right and left eye were averaged at each time point to obtain the values used in the analysis. In the worst-eye approach, the eye with the higher baseline IOP was followed throughout the course of the study.

As with the use of other antiglaucoma drugs, diminished responsiveness to TIMOPTIC after prolonged therapy has been reported in some patients. However, in one long-term study in which 96 patients have been followed for at least 3 years, no significant difference in mean IOP has been observed after initial stabilization.

TIMOPTIC is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; and hypersensitivity to any component of this product.

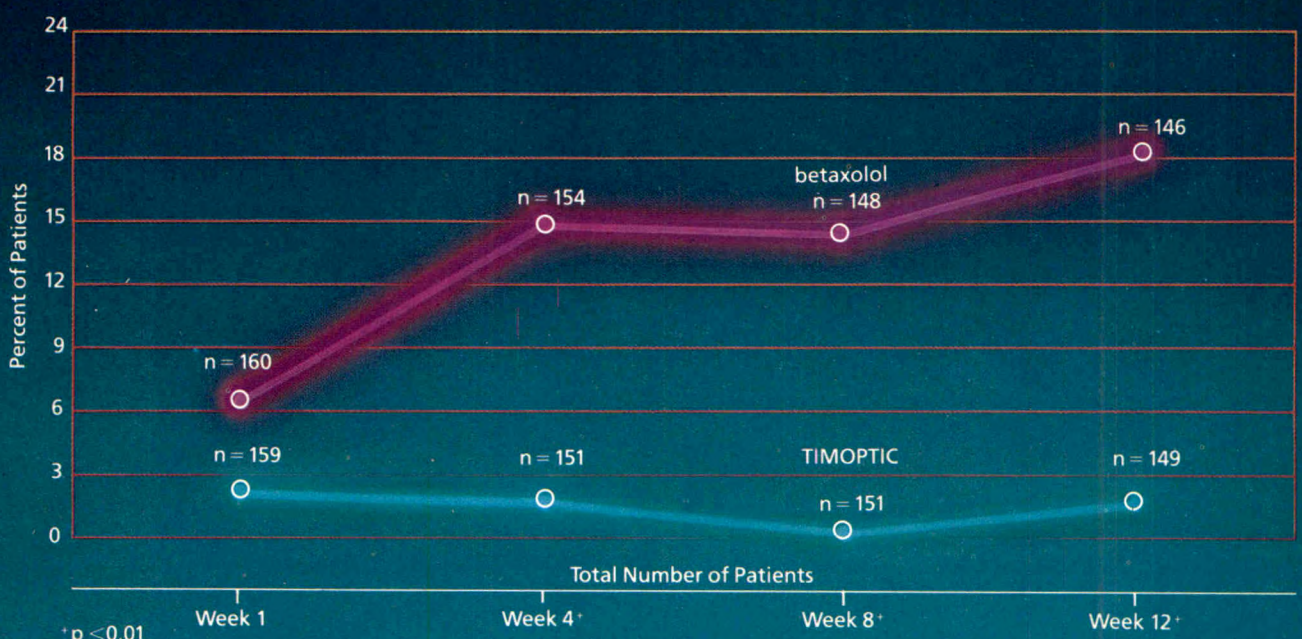
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PATIENTS EXHIBITING CHANGES IN INTRAOCULAR PRESSURE (FROM TREATED BASELINE) ≥ +5 mm Hg

Worst Eye



*p <0.01

Nearly 1 out of 5 patients treated with Betoptic showed an increase in IOP ≥ +5 mm Hg at week 12

For the majority of patients with chronic open-angle glaucoma or elevated IOP who are at sufficient risk to require therapy

TIMOPTIC®

(TIMOLOL MALEATE) MSD

STERILE OPHTHALMIC SOLUTION

O M A THERAPY TODAY

Before prescribing TIMOPTIC, please see the Brief Summary of Prescribing Information on the following page.

TIMOPTIC®

(TIMOLOL MALEATE) MSD

STERILE OPHTHALMIC SOLUTION

How to start patients on TIMOPTIC:
Usual starting dosage: one drop 0.25% TIMOPTIC in the affected eye(s) twice a day.

How to transfer from another topical ophthalmic beta-adrenergic blocking agent to TIMOPTIC:
1. On the first day, after proper dosing, discontinue the topical agent being used.
2. On the second day, start treatment with one drop of 0.25% TIMOPTIC in the affected eye(s) b.i.d.

How to transfer from a single antiglaucoma agent (other than a topical ophthalmic beta-adrenergic blocking agent) to TIMOPTIC:
1. On the first day, continue with the agent already being used and add one drop 0.25% TIMOPTIC in the affected eye(s) b.i.d.
2. On the second day, discontinue the previously used agent and continue with TIMOPTIC in the affected eye(s) b.i.d.

How to transfer from several concomitantly administered antiglaucoma agents to TIMOPTIC:
1. If any agent is an ophthalmic beta-adrenergic blocker, discontinue before starting TIMOPTIC.
2. Continue the other agents being used, but add one drop of 0.25% TIMOPTIC to the affected eye(s) b.i.d.
3. On the following day, discontinue one of the other antiglaucoma agents.
4. The remaining antiglaucoma agents may be decreased or discontinued according to the patient's response to treatment.

If clinical response is not adequate:
Dosage may be increased (from the 0.25% solution) by changing to one drop 0.5% TIMOPTIC twice a day in the affected eye(s). Dosages above one drop of 0.5% TIMOPTIC twice a day generally have not been shown to produce further reduction of IOP. If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s).

In patients with a history of severe cardiac disease, signs of cardiac failure should be watched for and pulse rates should be checked.

CONTRAINDICATIONS: TIMOPTIC is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to any component of this product.

WARNINGS: As with other topically applied ophthalmic drugs, this drug may be absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death in association with cardiac failure, have been reported following administration of TIMOPTIC (see CONTRAINDICATIONS).

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, TIMOPTIC should be discontinued.

Obstructive Pulmonary Disease: PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (e.g., CHRONIC BRONCHITIS, EMPHYSEMA) OF MILD OR MODERATE SEVERITY, BRONCHOSPASTIC DISEASE OR HISTORY OF BRONCHOSPASTIC DISEASE (OTHER THAN BRONCHIAL ASTHMA OR HISTORY OF BRONCHIAL ASTHMA, IN WHICH 'TIMOPTIC' IS CONTRAINDICATED, see CONTRAINDICATIONS), SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS, INCLUDING 'TIMOPTIC'. However, if TIMOPTIC is necessary in such patients, then the drug should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution to patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

PRECAUTIONS: *General:* Patients who are receiving a beta-adrenergic blocking agent orally and TIMOPTIC should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Patients should not receive two topical ophthalmic beta-adrenergic blocking agents concurrently.

Because of potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with TIMOPTIC, alternative therapy should be considered.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. TIMOPTIC has little or no effect on the pupil. When TIMOPTIC is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone.

As with the use of other antiglaucoma drugs, diminished responsiveness to TIMOPTIC® (Timolol Maleate MSD) after prolonged therapy has been reported in some patients. However, in one long-term study in which 96 patients have been followed for at least three years, no significant difference in mean intraocular pressure has been observed after initial stabilization.

Drug Interactions: Although TIMOPTIC used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with TIMOPTIC and epinephrine has been reported occasionally.

Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Caution should be used in the coadministration of beta-adrenergic blocking agents, such as TIMOPTIC, and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Animal Studies: No adverse ocular effects were observed in rabbits and dogs administered TIMOPTIC topically in studies lasting one and two years respectively.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year oral study of timolol maleate in rats, there was a statistically significant ($p < 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human oral dose* (1 mg/kg/day). Similar differences were not observed in rats administered oral doses equivalent to 25 or 100 times the maximum recommended human oral dose. In a lifetime oral study in mice, there were statistically significant ($p < 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages up to 60 mg timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p < 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/mL). In Ames tests, the highest concentrations of timolol employed, 5000 or 10,000 μg/plate, were associated with statistically significant elevations ($p < 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human oral dose.

Pregnancy: Pregnancy Category C: Teratogenicity studies with timolol in mice and rabbits at doses up to 50 mg/kg/day (50 times the maximum recommended human oral dose) showed no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (1,000 times the maximum recommended human oral dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 100 times the maximum recommended human oral dose, in this case without apparent maternotoxicity. There are no adequate and well-controlled studies in pregnant women. TIMOPTIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established by adequate and well-controlled studies.

ADVERSE REACTIONS: TIMOPTIC Ophthalmic Solution is usually well tolerated. The following adverse reactions have been reported either in clinical trials of up to three years' duration prior to release in 1978 or since the drug has been marketed.

BODY AS A WHOLE: Headache, asthenia, chest pain. CARDIOVASCULAR: Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, palpitation, cardiac arrest. DIGESTIVE: Nausea, diarrhea. NERVOUS SYSTEM/PSYCHIATRIC: Dizziness, depression, increase in signs and symptoms of myasthenia gravis, paresthesia. SKIN: Hypersensitivity, including localized and generalized rash, urticaria. RESPIRATORY: Bronchospasm (predominantly in patients with preexisting bronchospastic disease), respiratory failure, dyspnea, nasal congestion. ENDOCRINE: Masked symptoms of hypoglycemia in insulin-dependent diabetics (see WARNINGS). SPECIAL SENSES: Signs and symptoms of ocular irritation, including conjunctivitis, blepharitis, keratitis, blepharoptosis, decreased corneal sensitivity, visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis.

Causal Relationship Unknown: The following adverse effects have been reported, and a causal relationship to therapy with TIMOPTIC has not been established: *Body as a Whole:* Fatigue; *Cardiovascular:* Hypertension, pulmonary edema, worsening of angina pectoris; *Digestive:* Dyspepsia, anorexia, dry mouth; *Nervous System/Psychiatric:* Behavioral changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence, and other psychic disturbances; *Skin:* Alopecia; *Special Senses:* Aphakic cystoid macular edema; *Urogenital:* Retroperitoneal fibrosis, impotence.

The following additional adverse effects have been reported in clinical experience with oral timolol maleate and may be considered potential effects of ophthalmic timolol maleate: *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Edema, worsening of arterial insufficiency, Raynaud's phenomenon, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting; *Hematologic:* Nonthrombocytopenic purpura; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating, cold hands and feet; *Musculoskeletal:* Arthralgia, claudication; *Nervous System/Psychiatric:* Vertigo, local weakness, decreased libido, nightmares, insomnia, diminished concentration; *Respiratory:* Rales, cough, bronchial obstruction; *Special Senses:* Tinnitus, dry eyes; *Urogenital:* Urination difficulties.

Potential Adverse Effects: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents and may be considered potential effects of ophthalmic timolol maleate: *Digestive:* Mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Agranulocytosis, thrombocytopenic purpura; *Nervous System:* Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Urogenital:* Peyronie's disease.

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis sicca, otitis, and sclerosing serositis attributed to the beta-adrenergic receptor blocking agent practolol. This syndrome has not been reported with timolol maleate.

HOW SUPPLIED: TIMOPTIC Ophthalmic Solution, 0.25% and TIMOPTIC Ophthalmic Solution, 0.5%. Both are available in 2.5-mL, 5-mL, 10-mL, and 15-mL plastic OCUMETER® ophthalmic dispensers with a controlled drop tip. **Also Available:** Preservative-free TIMOPTIC in OCUDOSE® (Dispenser) Sterile Ophthalmic Unit-Dose Dispenser (see separate Prescribing Information).

Storage: Protect from light. Store at room temperature.

*The maximum recommended single oral dose is 30 mg of timolol. One drop of TIMOPTIC 0.5% contains about 1/150 of this dose, which is about 0.2 mg.

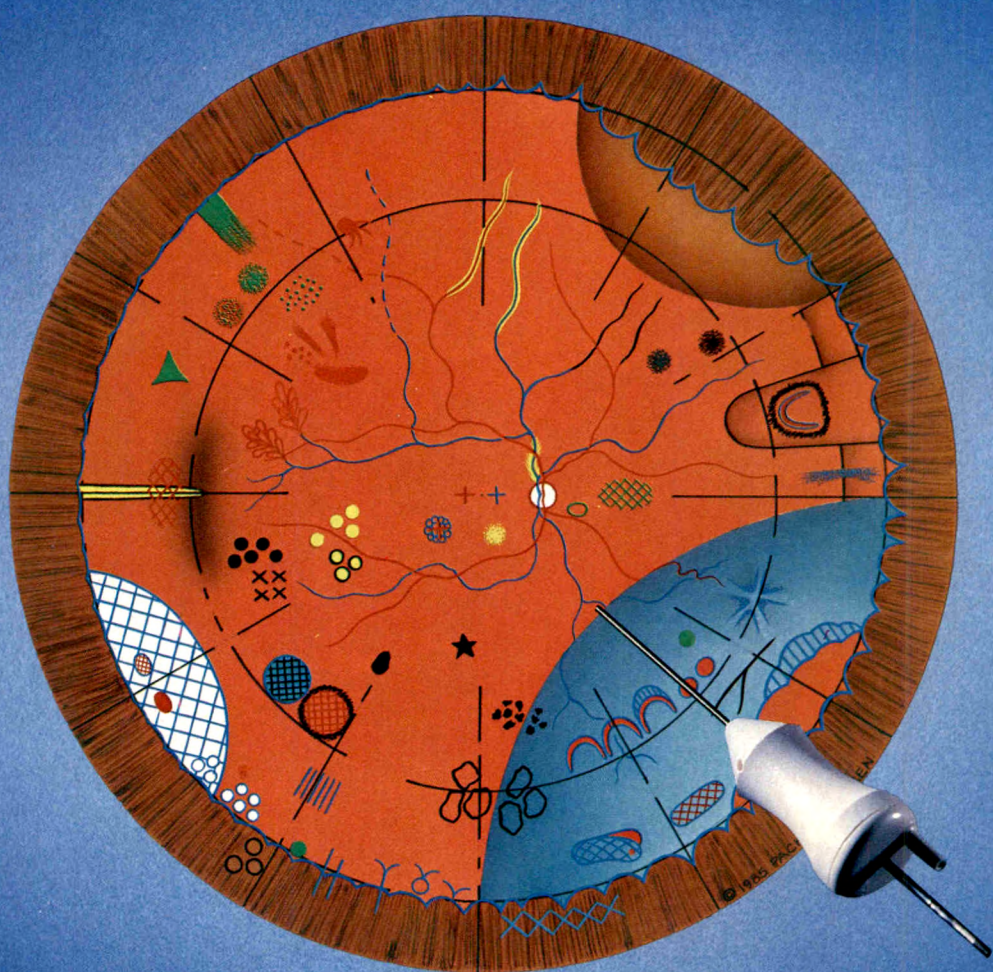
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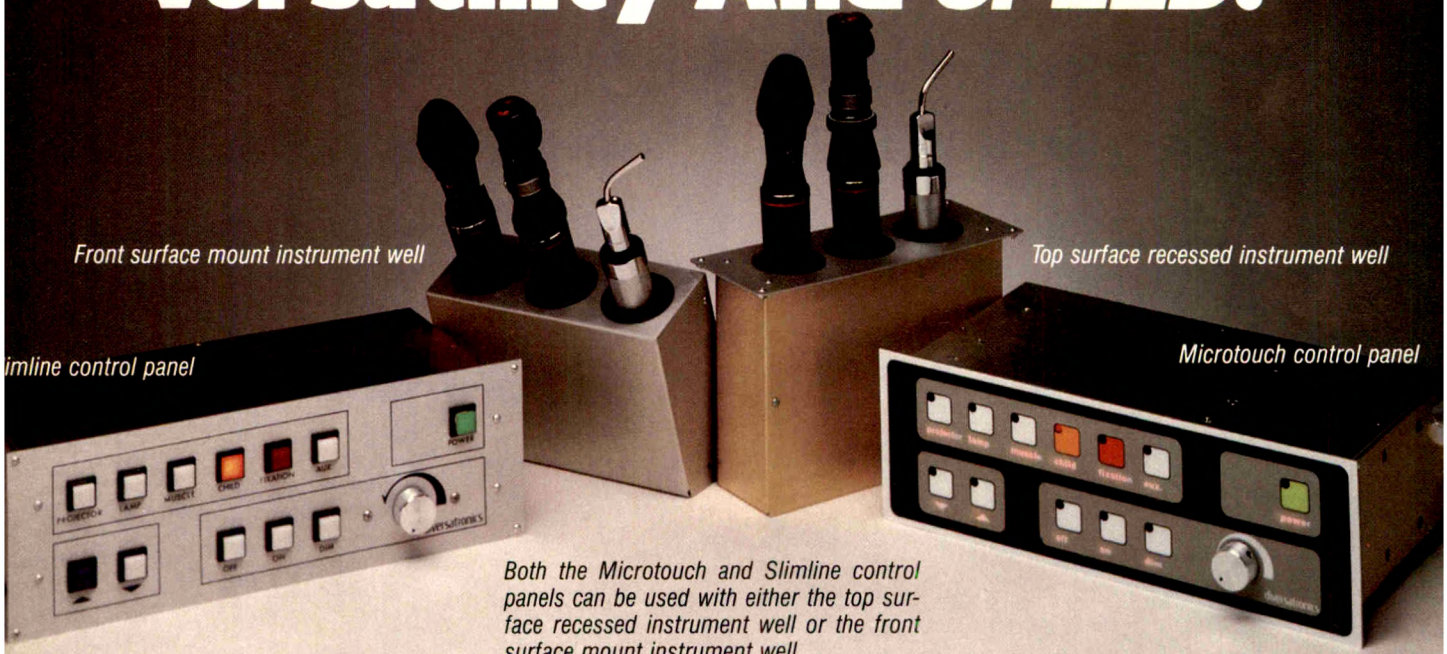
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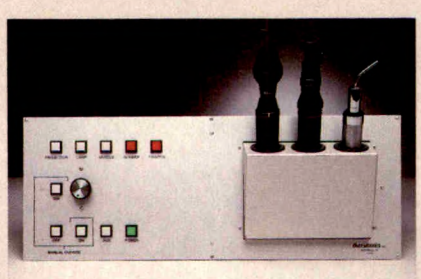
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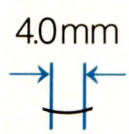
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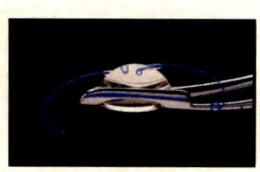
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A Familial Study of the Inheritance of HLA-B27-Positive Acute Anterior Uveitis

P. J. F. M. Derhaag, M.D., A. Linssen, Ph.D., N. Broekema, M.D.,
L. P. de Waal, Ph.D., and T. E. W. Feltkamp, Ph.D.

To determine whether factors besides HLA-B27 play a pathogenic role in acute anterior uveitis, we examined 152 first-degree relatives of 42 randomly selected HLA-B27-positive acute anterior uveitis patients. Nine relatives, all from different families, had acute anterior uveitis: eight were HLA-B27 positive and one was HLA-B27 negative. The prevalence of acute anterior uveitis in HLA-B27-positive first-degree relatives of HLA-B27-positive acute anterior uveitis patients was 13% (eight of 63). This is significantly more ($P < .0001$) than the frequency of 1% in the normal HLA-B27-positive Dutch population.

Ankylosing spondylitis was found in four of 38 (11%) HLA-B27-positive family members over the age of 45 years. This is also significantly more than the prevalence of 1% in a normal HLA-B27-positive Dutch population. Of these four relatives with ankylosing spondylitis, three also had acute anterior uveitis. It was remarkable that two of these four relatives had a proband who had no ankylosing spondylitis.

© American Journal of Ophthalmology 105:603–606, June, 1988

Immunopathologic Study of Vogt-Koyanagi-Harada Syndrome

Chi-Chao Chan, M.D., Alan G. Palestine, M.D., Toichiro Kuwabara, M.D.,
and Robert B. Nussenblatt, M.D.

We studied an enucleated eye from a patient with a 30-year history of Vogt-Koyanagi-Harada syndrome using both conventional and immunohistochemical techniques. Clinically, the eye was in the end stage of Vogt-Koyanagi-Harada syndrome, and was characterized by the absence of inflammation, large areas of chorioretinal scarring, and pigmentary changes. Histopathologic examination showed marked retinal gliosis, extensive chorioretinal adhesion and scar formation, migration of pigment into the retina, and severe retinal pigment epithelial changes. However, foci of mild to moderate nongranulomatous inflammation of the uvea were observed. These foci contained infiltrating cells that were mainly T lymphocytes with B lymphocyte aggregates at the center. Scattered macrophages were also noted in the uvea and retina. These findings suggest that both the cell-mediated and humoral immune arms may play roles in the pathogenesis of Vogt-Koyanagi-Harada syndrome.

© American Journal of Ophthalmology 105:607–611, June, 1988

Magnetic Resonance Imaging of Nonmetallic Orbital Foreign Bodies

W. Bruce Wilson, M.D., James N. Dreisbach, M.D., Daniel E. Lattin, M.D.,
and John C. Stears, M.D.

We studied a cadaver head model in which we inserted three orbital foreign bodies. We chose these foreign bodies because of their similarity to substances found in orbital trauma. Teflon and Lucite were used to represent synthetic materials, and dry pine was chosen as a type of organic material. Lucite is similar in radiographic density to plastics used in interior trim for automobiles and spectacle frames. While both orbital ultrasound and plain skull films failed to detect the foreign bodies consistently, both computed tomography and magnetic resonance imaging detected and localized the foreign bodies relatively well. Computed tomography was better in delineating shape and characterizing composition.

© American Journal of Ophthalmology 105:612–617, June, 1988

Transient Proliferative Diabetic Retinopathy During Intensified Insulin Treatment

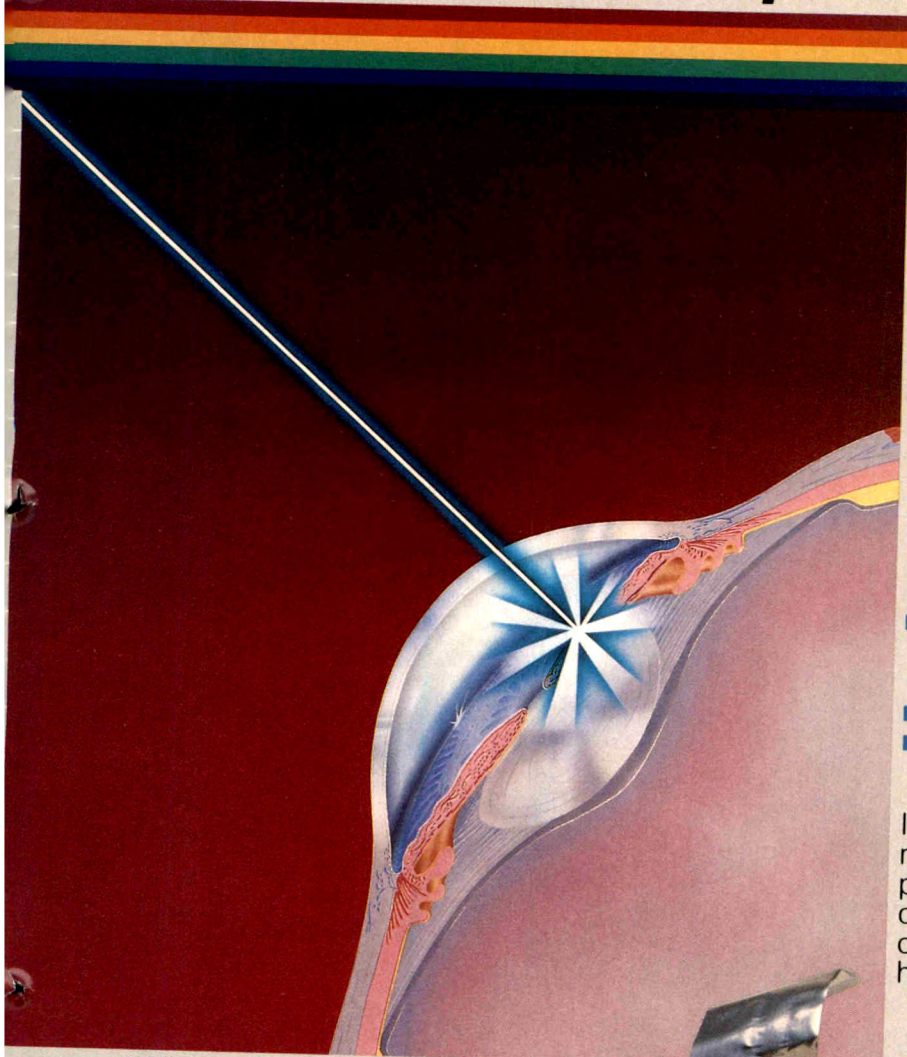
Ellen F. Rosenlund, M.D., Kirsti Haakens, M.D., Olaf Brinchmann-Hansen, M.D.,
Knut Dahl-Jørgensen, M.D., and Kristian F. Hanssen, M.D.

Two women aged 22 and 19 years who had had diabetes for 11 and four years, respectively, developed proliferative retinopathy after five to seven months of significantly improved metabolic control. They were participants in two separate prospective studies including 97 insulin-dependent patients. At inclusion, one patient showed minimal background retinopathy and the other showed no retinopathy. Their level of glycosylated hemoglobin was initially high (14.3% and 17.5%) but within five to six months had fallen by 5.7% and 7.5%. The improved metabolic control was obtained by home blood glucose monitoring and insulin pump in the older patient and by home blood glucose monitoring only in the other. By maintaining near normoglycemia, regression of the proliferative retinopathy was achieved. Photocoagulation was not performed. After five and two years of follow-up, respectively, only mild background retinopathy has been noted in both patients. We concluded that a significant lowering of blood glucose may provoke proliferative retinopathy and that sustained good metabolic control may reverse this retinopathy without photocoagulation.

© American Journal of Ophthalmology 105:618–625, June, 1988

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- Susceptible patients have experienced IOP spikes, visual field damage and/or vision loss
- Existing drugs do not consistently prevent or reduce IOP spikes

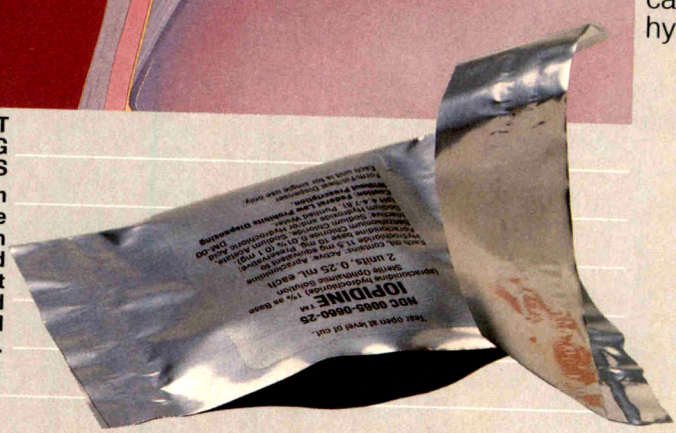
IOPIDINE resolves the problem

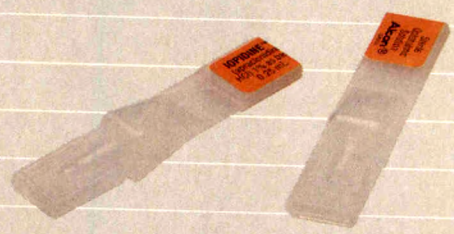
- Demonstrated significant IOP suppressing ability in double-masked, controlled clinical studies[1A, 1B, 2]
- Only two drops needed
- Well tolerated with minimal side effects[1A-3]

IOPIDINE™ ophthalmic solution has minimal effect on heart rate and blood pressure; however, caution should be observed in treating patients with severe cardiovascular disease including hypertension.

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Disclosure information appears on adjacent page.

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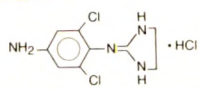
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DESCRIPTION: IOPIDINE ™ Ophthalmic Solution contains apraclonidine hydrochloride, an alpha adrenergic agonist, in a sterile isotonic solution for topical application to the eye. Apraclonidine hydrochloride is a white to off-white powder and is highly soluble in water. Its chemical name is 2-[(4-amino-2,6 dichlorophenyl) imino]imidazolidine monohydrochloride with an empirical formula of $C_9H_{11}Cl_3N_4$ and a molecular weight of 281.6. The chemical structure of apraclonidine hydrochloride is:



Each mL of IOPIDINE Ophthalmic Solution contains: Active – Apraclonidine hydrochloride 11.5 mg equivalent to apraclonidine base 10 mg; Preservative – Benzalkonium chloride 0.01%; Inactive – Sodium chloride, sodium acetate, sodium hydroxide and/or hydrochloric acid (pH 4.4-7.8) and purified water.

DM-00

CLINICAL PHARMACOLOGY

Apraclonidine is a relatively selective, alpha adrenergic agonist and does not have significant membrane stabilizing (local anesthetic) activity. When instilled into the eye, IOPIDINE (apraclonidine hydrochloride) Ophthalmic Solution has the action of reducing intraocular pressure. Ophthalmic apraclonidine has minimal effect on cardiovascular parameters.

Optic nerve head damage and visual field loss may result from an acute elevation in intraocular pressure that can occur after argon laser surgical procedures. Elevated intraocular pressure, whether acute or chronic in duration, is a major risk factor in the pathogenesis of visual field loss. The higher the peak or spike of intraocular pressure, the greater the likelihood of visual field loss and optic nerve damage especially in patients with previously compromised optic nerves. The onset of action with IOPIDINE Ophthalmic Solution can usually be noted within one hour and the maximum intraocular pressure reduction usually occurs three to five hours after application of a single dose. The precise mechanism of the ocular hypotensive action of IOPIDINE Ophthalmic Solution is not completely established at this time. Aqueous fluorophotometry studies in man suggest that its predominant action may be related to a reduction of aqueous formation.

Controlled clinical studies of patients requiring argon laser trabeculoplasty or argon laser iridotomy showed that IOPIDINE Ophthalmic Solution controlled or prevented the postsurgical intraocular pressure rise typically observed in patients after undergoing those procedures. After surgery, the mean intraocular pressure was 1.9 to 4.0 mmHg below the corresponding presurgical baseline pressure before IOPIDINE ™ Ophthalmic Solution treatment. With placebo treatment, postsurgical pressures were 2.5 to 8.4 mmHg higher than their corresponding presurgical baselines. Overall, only 2% of patients treated with IOPIDINE Ophthalmic Solution had severe intraocular pressure elevations (spike ≥ 10 mmHg) during the first three hours after laser surgery, whereas 21% of placebo-treated patients responded with severe pressure spikes (Table 1). Of the patients that experienced a pressure spike after surgery, the peak intraocular pressure was above 30 mmHg in most patients (Table 2) and was above 50 mmHg in seven placebo-treated patients and one IOPIDINE Ophthalmic Solution-treated patient.

Table 1
Incidence of Intraocular Pressure Spikes ≥ 10 mmHg

			Treatment			
			Apraclonidine		Placebo	
Study	Laser Procedure	P-Value	N[a]	(%)	N[a]	(%)
1	Overall	<0.05	0/51	(0%)	10/45	(22%)
2	Overall	<0.05	2/58	(3%)	12/61	(20%)
1	Trabeculoplasty	<0.05	0/40	(0%)	6/35	(17%)
2	Trabeculoplasty	=0.06	2/41	(5%)	8/42	(19%)
1	Iridotomy	<0.05	0/11	(0%)	4/10	(40%)
2	Iridotomy	=0.05	0/17	(0%)	4/19	(21%)

[a]N = Number Spikes / Number Eyes.

Table 2
Magnitude of Postsurgical Intraocular Pressure in Trabeculoplasty and Iridotomy Patients With Severe Pressure Spikes ≥ 10 mmHg

		Maximum Postsurgical Intraocular Pressure (mmHg)			
Treatment	Total Spikes	20-29 mmHg	30-39 mmHg	40-49 mmHg	> 50 mmHg
Apraclonidine	2	0	0	1	1
Placebo	22	1	10	4	7

INDICATIONS AND USAGE

IOPIDINE (apraclonidine hydrochloride) Ophthalmic Solution is indicated to control or prevent postsurgical elevations in intraocular pressure that occur in patients after argon laser trabeculoplasty or argon laser iridotomy.

CONTRAINDICATION

Hypersensitivity to any component of this medication or to clonidine.

PRECAUTIONS

General

Since IOPIDINE Ophthalmic Solution is a potent depressor of intraocular pressure, patients who develop exaggerated reductions in intraocular pressure should be closely monitored.

Although the acute administration of two drops of IOPIDINE ™ Ophthalmic Solution has minimal effect on heart rate or blood pressure in clinical studies evaluating patients undergoing anterior segment laser surgery, the preclinical pharmacologic profile of this drug suggests that caution should be observed in treating patients with severe cardiovascular disease including hypertension.

The possibility of a vasovagal attack occurring during laser surgery should be considered and caution used in patients with history of such episodes.

Topical ocular administration of two drops of 0.5%, 1.0% and 1.5% IOPIDINE Ophthalmic Solution to New Zealand Albino rabbits three times daily for one month resulted in sporadic and transient instances of minimal corneal cloudiness in the 1.5% group only. No histopathological changes were noted in those eyes. No adverse ocular effects were observed in cynomolgus monkeys treated with two drops of 1.5% IOPIDINE Ophthalmic Solution applied three times daily for three months. No corneal changes were observed in 320 humans given at least one dose of 1.0% IOPIDINE Ophthalmic Solution.

Drug Interactions

Interactions with other agents have not been investigated.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a variety of *in vitro* cell assays, apraclonidine was nonmutagenic. Studies addressing carcinogenesis and the impairment of fertility have not been conducted.

Pregnancy Category C

There are no adequate and well controlled studies of IOPIDINE Ophthalmic Solution in pregnant women. Animal reproduction studies have not been conducted with apraclonidine hydrochloride. This medication should be used in pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers

It is not known if topically applied IOPIDINE Ophthalmic Solution is excreted in human milk. A decision should be considered to discontinue nursing temporarily for the one day on which IOPIDINE Ophthalmic Solution is used.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The following adverse events were reported in association with the use of IOPIDINE Ophthalmic Solution in laser surgery: upper lid elevation (1.3%), conjunctival blanching (0.4%) and mydriasis (0.4%).

The following adverse events were observed in investigational studies dosing IOPIDINE Ophthalmic Solution once or twice daily for up to 28 days in nonlaser studies:

OCULAR: Conjunctival blanching, upper lid elevation, mydriasis, burning, discomfort, foreign body sensation, dryness, itching, hypotony, blurred or dimmed vision, allergic response, conjunctival microhemorrhage

GASTROINTESTINAL: Abdominal pain, diarrhea, stomach discomfort, emesis

CARDIOVASCULAR: Bradycardia, vasovagal attack, palpitations, orthostatic episode

CENTRAL NERVOUS SYSTEM: Insomnia, dream disturbances, irritability, decreased libido

OTHER: Taste abnormalities, dry mouth, nasal burning or dryness, headache, head cold sensation, chest heaviness or burning, clammy or sweaty palms, body heat sensation, shortness of breath, increased pharyngeal secretion, extremity pain or numbness, fatigue, paresthesia, pruritus not associated with rash

OVERDOSAGE

No information is available on overdosage in humans. The oral LD_{50} of the drug ranged from 3-8 mg/kg in mice and 38-107 mg/kg in rats. The intravenous LD_{50} of the drug ranged from 6-9 mg/kg in mice and 9-21 mg/kg in rats. LD_{50} values in these ranges are indicative of a drug with a high degree of toxicity.

DOSAGE AND ADMINISTRATION

One drop of IOPIDINE Ophthalmic Solution should be instilled in the scheduled operative eye one hour before initiating anterior segment laser surgery and a second drop should be instilled to the same eye immediately upon completion of the laser surgical procedure.

HOW SUPPLIED

IOPIDINE (apraclonidine hydrochloride) Ophthalmic Solution 1% as base is a sterile, isotonic, aqueous solution containing apraclonidine hydrochloride. Supplied as follows: 0.25 mL in plastic ophthalmic dispensers, packaged two per pouch. These dispensers are enclosed in a foil overwrap as an added barrier to evaporation.

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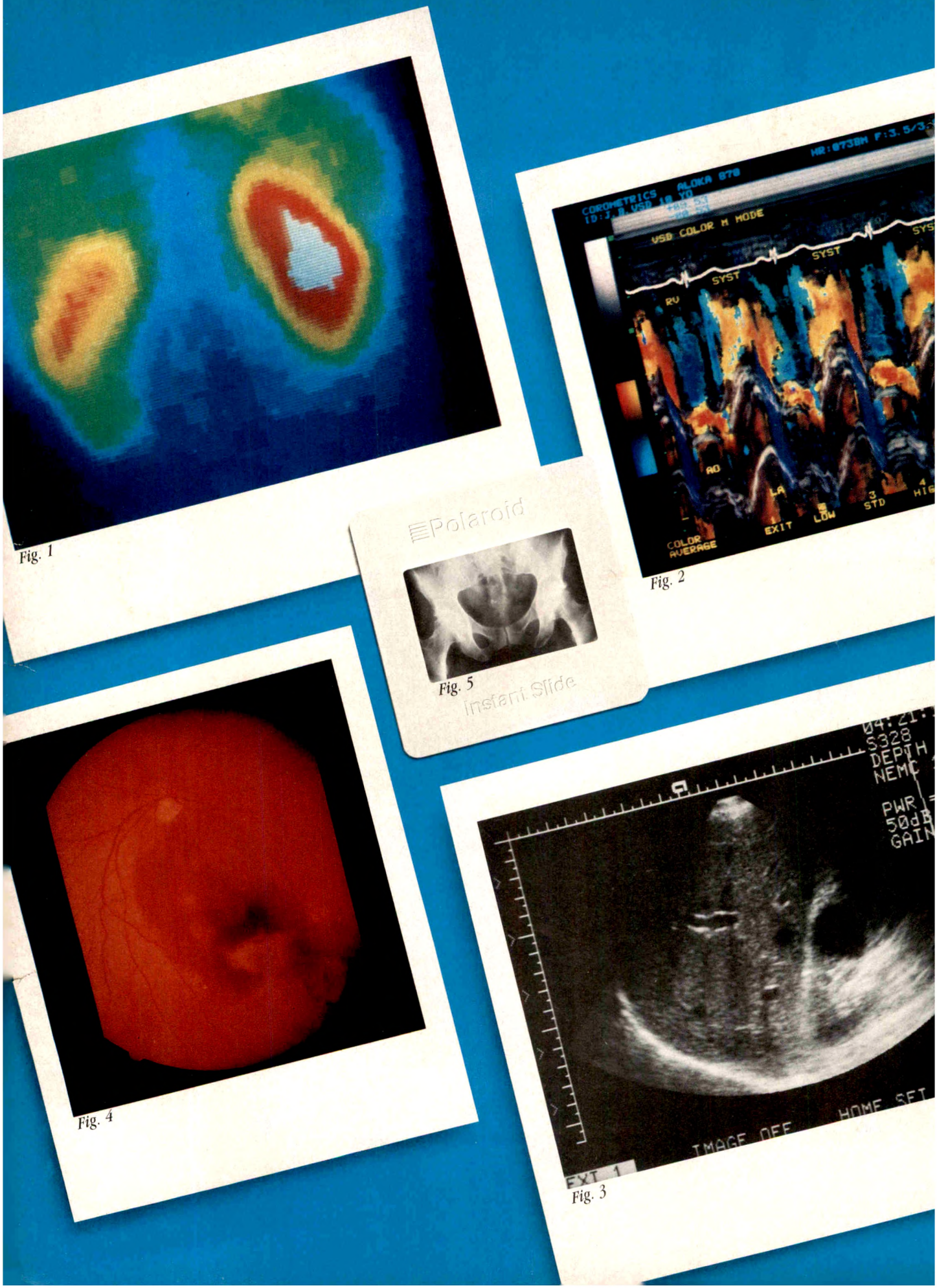


Fig. 1

Fig. 2

Fig. 5

Fig. 4

Fig. 3

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Corneal Fistulas and Their Management

Mark J. Mannis, M.D., James Ruben, M.D., and Linda Wedemeyer, M.D.

We reviewed three representative cases of chronic corneal fistula formation and provide a systematic approach to the assessment and therapeutic alternatives for this problem. In two of our patients, the fistula was managed surgically. The third patient developed endophthalmitis, which resulted in loss of light perception. Chronic corneal fistulization is a rare clinical entity resulting from malapposition of corneal tissue after traumatic, surgical, or infectious perforation. Fistulas may result in prolonged or recurrent hypotony, peripheral anterior synechia formation, or endophthalmitis. Accurate assessment of the risks associated with corneal fistula formation takes into account the type of fistula, its location in the cornea, and the condition of the ocular adnexae. We reviewed the risk factors that will determine the urgency and type of therapy used.

© American Journal of Ophthalmology 105:626–631, June, 1988

Infected vs Sterile Corneal Infiltrates in Contact Lens Wearers

Raymond M. Stein, M.D., Thomas E. Clinch, M.D., Elisabeth J. Cohen, M.D., Gail I. Genvert, M.D., Juan J. Arentsen, M.D., and Peter R. Laibson, M.D.

We examined 50 patients to determine whether differences exist between the initial clinical signs and symptoms associated with infected vs sterile corneal infiltrates. A detailed history regarding contact lens use and ocular symptoms was taken, after which a careful slit-lamp examination was performed. The ocular findings were correlated with the results of corneal cultures. Increased pain ($P < .001$), discharge ($P < .0001$), epithelial staining ($P < .0001$), and anterior chamber reaction ($P < .0001$) were associated with infected ulcers. Sterile infiltrates were usually smaller; multiple or arcuate; and without significant pain, epithelial staining, or anterior chamber reaction.

© American Journal of Ophthalmology 105:632–636, June, 1988

The Effect of Suture Removal on Postkeratoplasty Astigmatism

Perry S. Binder, M.D.

I followed up for a minimum of six months 439 eyes that had undergone corneal transplantation using a suturing technique consisting of eight interrupted 10-0 and a single, continuous, 16-bite 11-0 nylon suture. All sutures were removed from 188 eyes an average of 20 months after surgery. After suture removal, 64 corneas had an increase of astigmatism greater than 0.5 diopter, 79 eyes showed a decrease in astigmatism greater than 0.5 diopter, and 42 corneas had no change in astigmatism. The mean astigmatism before suture removal was 3.7 diopters, and the mean astigmatism after suture removal was 3.5 diopters. There was no apparent difference in postkeratoplasty astigmatism with donor corneal diameters 0.25 to 0.75 mm greater in diameter than the recipient diameters, or with different host diseases. The longer the sutures were left in place after surgery, the smaller the quantitative change in astigmatism after suture removal. The complications of this technique were no different from other currently used suture techniques.

© American Journal of Ophthalmology 105:637–645, June, 1988

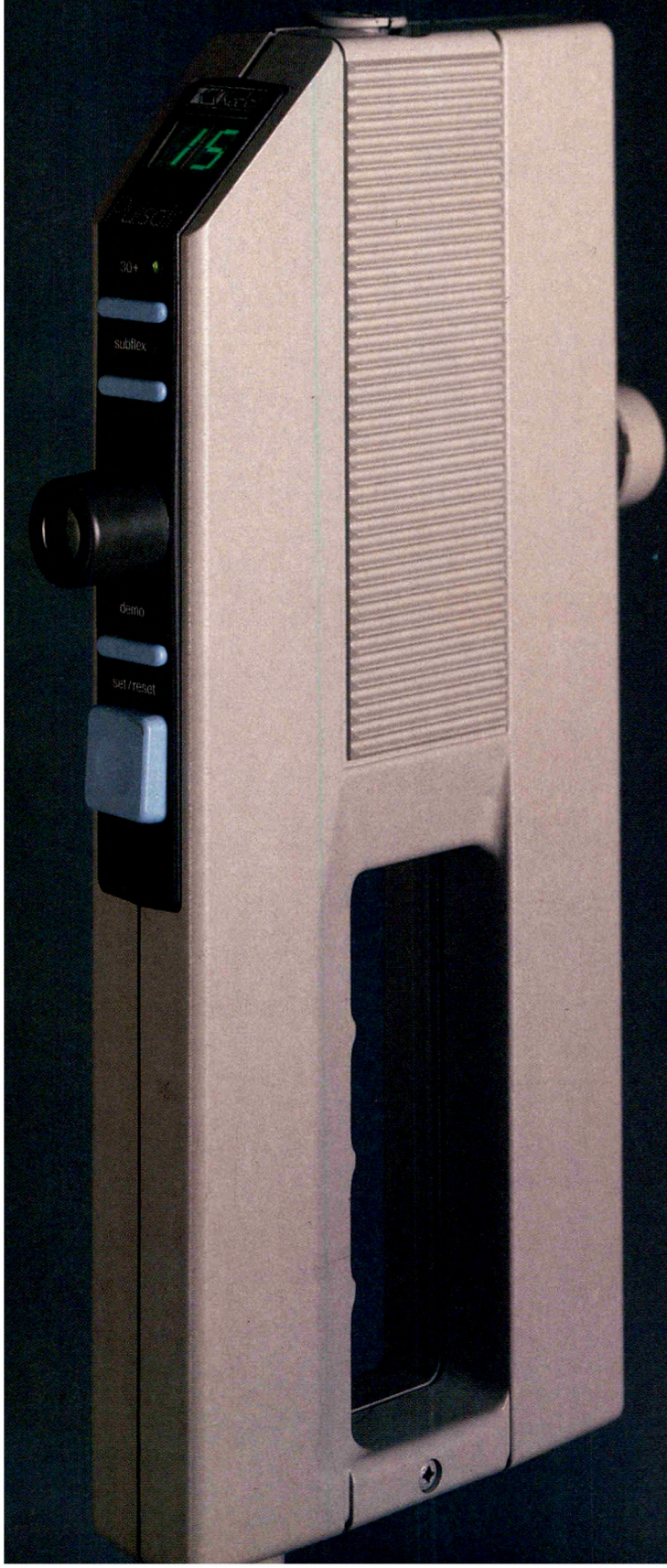
A Study of Race Matching Between Donor and Recipient in Corneal Transplantation

David C. Musch, Ph.D., Roger F. Meyer, M.D., Alan Sugar, M.D., and H. Kaz Soong, M.D.

We investigated the influence of a racial match or mismatch between the corneal donor and recipient on the risk of endothelial rejection and subsequent graft failure in 998 corneal transplant recipients. Actuarial survival analysis showed no significant difference in the cumulative risk of endothelial rejection between the 676 race-matched and 322 race-mismatched recipients. Recipients who had preoperative factors that placed them at a higher risk of endothelial rejection ($n = 208$) also were not subject to a higher incidence of endothelial rejection if they received race-mismatched tissue. Graft failure after endothelial rejection was not found to differ among race-matched or -mismatched groups.

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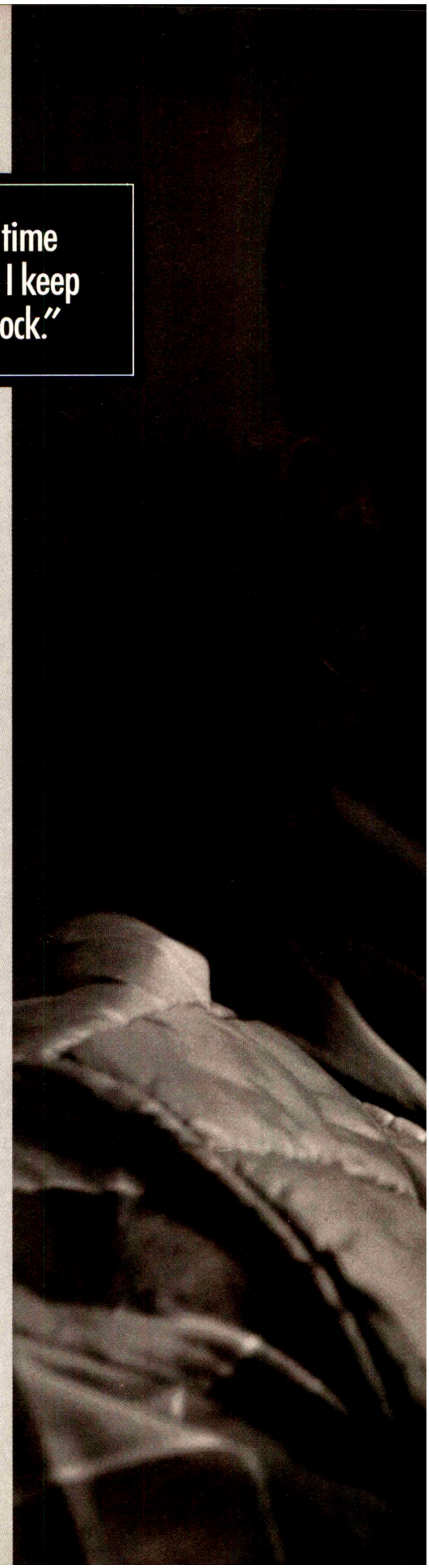
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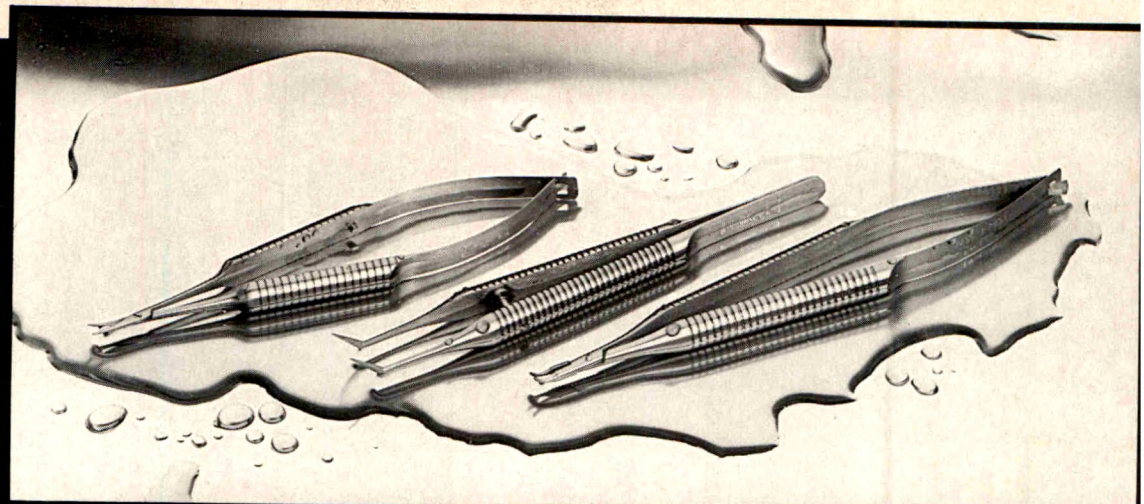
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2. David R. Ober M. Foerster Ret al. The efficacy of once-daily beta-blockers for glaucoma treatment. Am J. Ophthalmol 1987;104:443
3. Levobunolol Clinical Study Group. Levobunolol: A beta-adrenoceptor antagonist effective in the long-term treatment of glaucoma. Ophthalmology 1985;92:1271.

Brief Summary of Prescribing Information

INDICATIONS AND USAGE: BETAGAN Liquifilm sterile ophthalmic solution has been shown to be effective in lowering intraocular pressure and may be used in patients with chronic open-angle glaucoma or ocular hypertension. **CONTRAINDICATIONS:** BETAGAN is contraindicated in those individuals with bronchial asthma or with a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second and third degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; or hypersensitivity to any component of this product. **WARNINGS:** As with other topically applied ophthalmic drugs, BETAGAN may be absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported with topical application of beta-adrenergic blocking agents (see CONTRAINDICATIONS). *Cardiac Failure:* Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. *In Patients Without a History of Cardiac Failure:* Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, BETAGAN should be discontinued. *Non-allergic Bronchospasm:* In patients with non-allergic bronchospasm or with a history of non-allergic bronchospasm (e.g., chronic bronchitis, emphysema), BETAGAN should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of $beta_2$ receptors. *Major Surgery:* The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. For these reasons, in patients undergoing elective surgery, gradual withdrawal of beta-adrenergic receptor blocking agents may be appropriate. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol (see OVERDOSAGE). *Diabetes Mellitus:* Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia. *Thyrotoxicosis:* Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm. Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people. **PRECAUTIONS:** ***General:*** **BETAGAN®** (levobunolol HCl) 0.5% Liquifilm® sterile ophthalmic solution should be used with caution in patients with known hypersensitivity to other beta-adrenoceptor blocking agents. Use with caution in patients with known diminished pulmonary function. In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. BETAGAN has little or no effect on the pupil. When BETAGAN is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone. *Muscle Weakness:* Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalized weakness). *Drug Interactions:* BETAGAN should be used with caution in patients who are receiving a beta-adrenergic blocking agent orally, because of the potential for additive effects on systemic beta-blockade. Although BETAGAN used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with BETAGAN and epinephrine may occur. Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension. *Animal Studies:* No adverse ocular effects were observed in rabbits administered BETAGAN topically in studies lasting one year in concentrations up to 10 times the human dose concentration. *Carcinogenesis, mutagenesis, impairment of fertility:* In a lifetime oral study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign leiomyomas in female mice at 200 mg/kg/day (14,000 times the recommended human dose for glaucoma), but not at 12 or 50 mg/ kg/day (850 and 3,500 times the human dose). In a two-year oral study of levobunolol HCl in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of benign hepatomas in male rats administered 12,800 times the recommended human dose for glaucoma. Similar differences were not observed in rats administered oral doses equivalent to 350 times to 2,000 times the recommended human dose for glaucoma. Levobunolol did not show evidence of mutagenic activity in a battery of microbiological and mammalian *in vitro* and *in vivo* assays. Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 1,800 times the recommended human dose for glaucoma. *Pregnancy Category C:* Fetotoxicity (as evidenced by a greater number of resorption sites) has been observed in rabbits when doses of levobunolol HCl equivalent to 200 and 700 times the recommended dose for the treatment of glaucoma were given. No fetotoxic effects have been observed in similar studies with rats at up to 1,800 times the human dose for glaucoma. Teratogenic studies with levobunolol in rats at doses up to 25 mg/kg/day (1,800 times the recommended human dose for glaucoma) showed no evidence of fetal malformations. There were no adverse effects on postnatal development of offspring. It appears when results from studies using rats and studies with other beta-adrenergic blockers are examined, that the rabbit may be a particularly sensitive species. There are no adequate and well-controlled studies in pregnant women. BETAGAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Nursing Mothers:* It is not known whether this drug is excreted in human milk. Systemic beta-blockers and topical timolol maleate are known to be excreted in human milk. Caution should be exercised when BETAGAN is administered to a nursing woman. *Pediatric Use:* Safety and effectiveness in children have not been established. **ADVERSE REACTIONS:** In clinical trials the use of BETAGAN has been associated with transient ocular burning and stinging in about one in four patients, and with blepharoconjunctivitis in about one in 20 patients. Decreases in heart rate and blood pressure have been reported occasionally (see CONTRAINDICATIONS and WARNINGS). The following adverse effects have been reported rarely with the use of BETAGAN: Iridocyclitis, headache, transient ataxia, dizziness, lethargy, urticaria and pruritus. Decreased corneal sensitivity has been noted in a small number of patients. Although levobunolol has minimal membrane-stabilizing activity, there remains a possibility of decreased corneal sensitivity after prolonged use. The following additional adverse reactions have been reported with ophthalmic use of $beta_1$ and $beta_2$ (non-selective) adrenergic receptor blocking agents: BODY AS A WHOLE: Headache. CARDIOVASCULAR; Arrhythmia, syncope, heart block, cerebral vascular accident, cerebral ischemia, congestive heart failure, palpitation. DIGESTIVE: Nausea. PSYCHIATRIC: Depression. SKIN: Hypersensitivity, including localized and generalized rash. RESPIRATORY: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure. ENDOCRINE: Masked symptoms of hypoglycemia in insulin-dependent diabetics (see WARNINGS). SPECIAL SENSES: Signs and symptoms of keratitis, blepharoptosis, visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis. Other reactions associated with the oral use of non-selective adrenergic receptor blocking agents should be considered potential effects with ophthalmic use of these agents.

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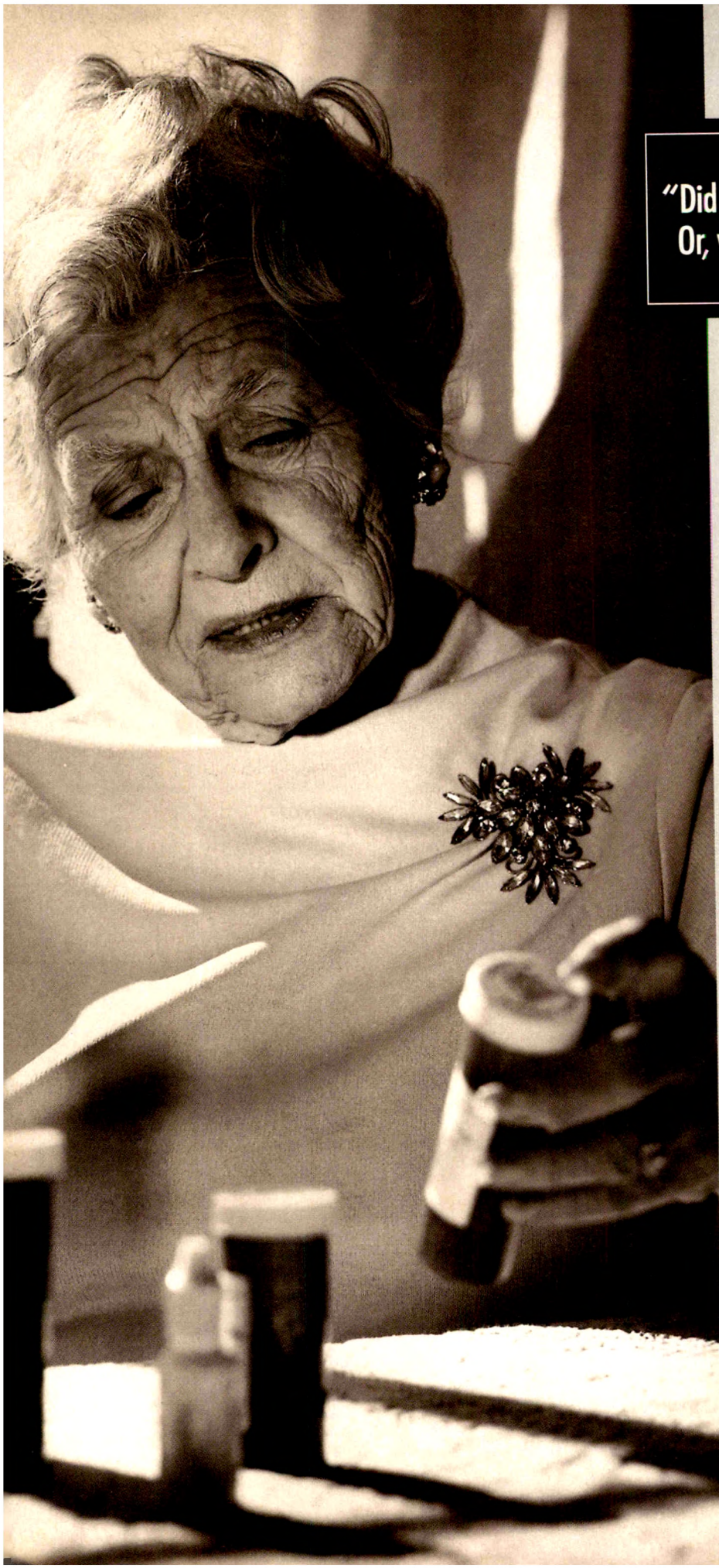
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AMERICAN JOURNAL OF OPHTHALMOLOGY®

VOLUME 105 NUMBER 6 JUNE, 1988

A Proposed Mild Type of Acute Retinal Necrosis Syndrome

Toshihiko Matsuo, M.D., Tadashi Nakayama, M.D., Tetsuro Koyama, M.D., Masaya Koyama, M.D., and Nobuhiko Matsuo, M.D.

Six patients had peripheral to midperipheral pale yellow retinal exudates typical of acute retinal necrosis syndrome but which extended gradually to the posterior pole and remained isolated without becoming confluent. These exudates resulted in localized retinochoroidal degeneration without retinal detachment, in contrast to acute retinal necrosis syndrome. Antibody titers in aqueous humor were increased to varicella-zoster virus in some of the patients examined. The findings led us to hypothesize that this mild, self-limiting course is one of the natural developments of acute retinal necrosis syndrome, although somewhat modified by corticosteroid or acyclovir therapy, and that acute retinal necrosis syndrome consists of varying degrees of severity from mild to fulminant types.

ACUTE RETINAL NECROSIS syndrome is characterized by peripheral to midperipheral pale yellow retinal exudates associated with vitreous opacity and anterior uveitis. These exudates soon become confluent at 360 degrees and extend to the posterior pole, finally resulting in retinal detachment.[1-3] Varicella-zoster virus and herpes simplex virus type 1 are the causative agents of acute retinal necrosis syndrome.[4,5] Acute retinal necrosis syndrome has generally been described as taking a fulminant course and is usually resistant to various modes of treatment such as antivirals, corticosteroids, or anticoagulants.

We studied six patients, including two described previously,[6,7] who showed peripheral to midperipheral pale yellow retinal exudates associated with vitreous opacities and anterior uveitis, typical of acute retinal necrosis syndrome. These exudates, in contrast to those described previously in acute retinal necrosis syndrome, extended gradually to the posterior pole. They resulted in localized retinochoroidal degeneration without causing retinal detachment before becoming confluent and involving the posterior pole. Antibody titers in the aqueous humor were increased to varicella-zoster virus in three of the six patients examined.

Case Reports

Case 1

A 44-year-old man noticed blurred vision in his right eye. On admission, best corrected visual acuity was R.E.: 20/20 and L.E.: 20/15. Intraocular pressure was 27 mm Hg in the right eye and 15 mm Hg in the left eye. Slit-lamp biomicroscopic examination showed mild ciliary injection, fine keratic precipitates, numerous aqueous cells, 1+ aqueous flare, and diffuse vitreous opacities in the right eye. The anterior segments in the left eye were normal. In the right eye ophthalmoscopic examination showed a blurred, hyperemic disk, with isolated pale yellow retinal exudates with perivenous hemorrhage scattered in the midperiphery to periphery (Fig. 1). The left fundus showed a degenerative lesion in the inferotemporal periphery. The patient underwent a

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Reprint requests to Toshihiko Matsuo, M.D., Department of Ophthalmology, Okayama University Medical School, 2-5-1 Shikata-cho, Okayama City, Okayama 700, Japan.

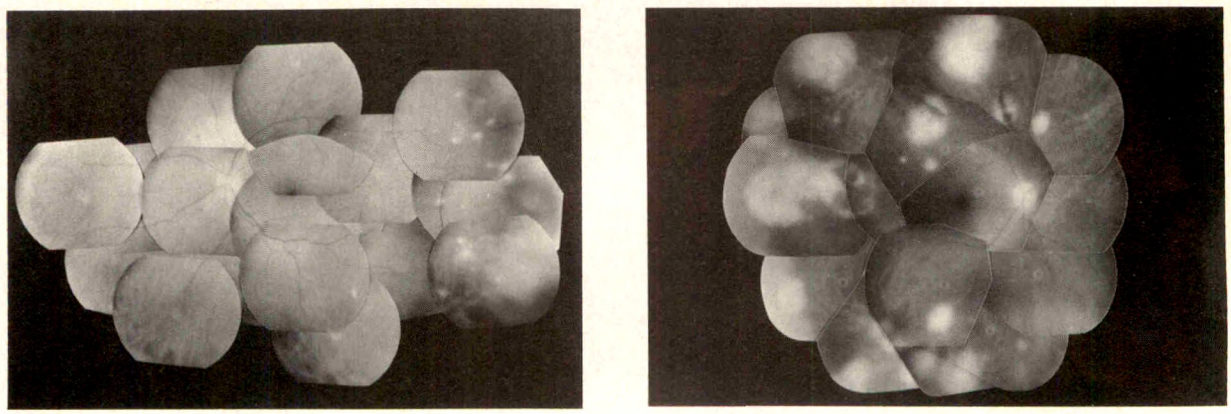


Fig. 1 (Matsuo and associates). Case 1. Montages of right fundus (left) and left fundus (right) at initial examination show isolated retinal exudates.

three-day course of double filtration plasmapheresis with a total filtrated volume of 5,100 ml exchanged with 1,300 ml of 5% albumin electrolyte solution. Drip infusion of prednisolone (200 mg/day) was administered concurrently, and the dose was gradually tapered for a total dosage of 2,820 mg. The exudates remained stationary and finally resulted in localized retinochoroidal degeneration.

The patient was well for the following two years but then developed blurred vision and injection in the left eye. On admission, the best corrected visual acuity was R.E.: 20/20 and L.E.: 20/15. The intraocular pressure was 14 mm Hg in the right eye and 30 mm Hg in the left eye. Slit-lamp biomicroscopy of the left eye showed mutton-fat keratic precipitates, fine precipitates, 2+ aqueous cells, 1+ aqueous flare, and 1+ cells in the anterior vitreous. The anterior segments in the right eye were unremarkable. Ophthalmoscopy disclosed isolated retinochoroidal degenerative areas in the right eye, with pale yellow exudates in the temporal midperiphery to periphery in the left eye (Fig. 1). Drip infusion of prednisolone (200 mg/day) was started. The dose was gradually tapered for a total dosage of 2,210 mg. A course of acyclovir (500 mg/day) was given concurrently for 15 days. The exudates extended gradually to the posterior pole and finally resulted in retinochoroidal degeneration before becoming confluent at 360 degrees.

Case 2

A 34-year-old woman had blurred vision, floating spots, and injection in the left eye. On admission, best corrected visual acuity was R.E.: 20/15 and L.E.: 20/40. Intraocular pressure was 15 mm Hg in the right eye and 8 mm Hg in the left eye. The anterior segments and fundus in the right eye were unremarkable. The left eye showed fine keratic precipitates, 3+ aqueous cells, marked vitreous opacity, and isolated temporal and superior peripheral pale yellow retinal exudates. Drip infusion of prednisolone (100 mg/day) was started. The dose was tapered for a total of 1,365 mg. The exudates resulted in localized peripheral retinochoroidal degeneration (Fig. 2) and best corrected visual acuity was L.E.: 20/15.

Case 3

An 85-year-old woman developed blurred vision and floating spots in the left eye. On examination one month later, best corrected visual acuity was R.E.: 20/20 and L.E.: 20/1000; the intraocular pressure was 14 mm Hg in the right eye and 11 mm Hg in the left eye. The right eye had an incipient cataract. The left eye showed fine keratic precipitates, 2+ aqueous

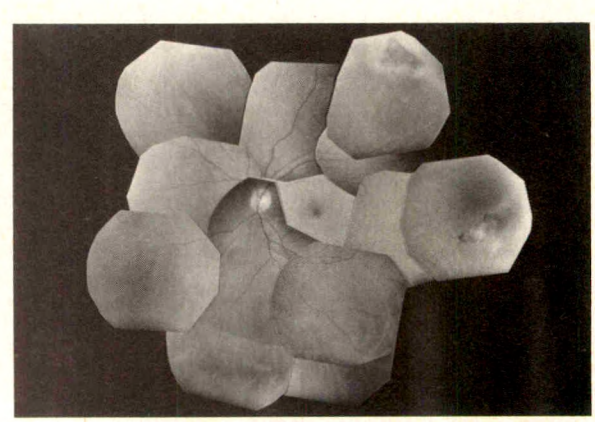


Fig. 2 (Matsuo and associates). Case 2. Montage of left fundus three years after onset shows localized peripheral degeneration.

cells and flare, and marked dense vitreous opacity. The disk was hyperemic. The retinal arteries were white-sheathed, and midperipheral pale yellow retinal exudates were confluent clockwise from the 10 o'clock to the 5 o'clock meridians. Drip infusion of prednisolone (100 mg/day) for a total dose of 1,080 mg and acyclovir (500 mg/day) for seven days were started. One month later, the exudates progressed to retinochoroidal degeneration. The vitreous opacity was reduced and the visual acuity in the left eye returned to 20/70.

Case 4

A 26-year-old woman, who had chickenpox in the eighth month of pregnancy, developed blurred vision and injection in the right eye. Best corrected visual acuity was R.E.: 20/200 and L.E.: 20/30. Intraocular pressure was 10 mm Hg in both eyes. The right eye showed ciliary injection, 3+ mutton-fat keratic precipitates, numerous fine keratic precipitates, 3+ aqueous cells, 2+ aqueous flare, 2+ anterior vitreous cells, and pale yellow retinal exudates confluent at the 360-degree periphery. The left eye had fine keratic precipitates, 2+ aqueous cells, 1+ aqueous flare, 1+ anterior vitreous cells, and isolated retinal exudates with perivasculitis located in the inferotemporal, inferior, and nasoinferior periphery. After the delivery of a full-term healthy baby by a cesarean section ten days later, drip infusion of prednisolone (200 mg/day) for a total dose of 2,210 mg and acyclovir (500 mg/day) for seven days were started. The exudates remained stationary and finally resulted in retinochoroidal degeneration. Visual acuity returned to R.E.: 20/15 and L.E.: 20/15.

Case 5

A 67-year-old woman developed injection and blurred vision in the left eye. Best corrected visual acuity was R.E.: 20/15 and L.E.: 20/70. Intraocular pressure was 19 mm Hg in the right eye and 13 mm Hg in the left eye. The anterior segments and fundus were unremarkable. The left eye showed ciliary injection, some fine keratic precipitates, 2+aqueous cells, marked vitreous opacity, and pale yellow retinal exudates in the inferior portion of the midperiphery to periphery. Drip infusion of prednisolone (200 mg/day) was gradually tapered and acyclovir (750 mg/day) for nine days was started. The retinal exudates remained stationary and resulted in retinochoroidal degeneration with epiretinal membrane formation (Fig. 3). Visual acuity in the left eye was again 20/20.

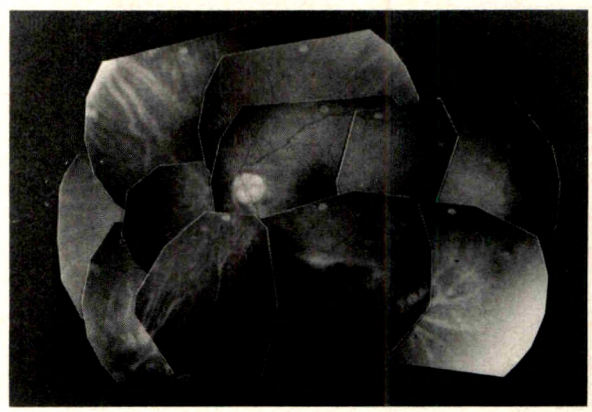


Fig. 3 (Matsuo and associates). Case 5. Left fundus six months after onset shows retinochoroidal degeneration with epiretinal membrane formation in the inferior portion of the midperiphery.

Case 6

A 23-year-old woman had blurred vision and injection in the right eye. Best corrected visual acuity was R.E.: 20/15 and L.E.: 20/20. Intraocular pressure was 9 mm Hg in the right eye and 8 mm Hg in the left eye. The right eye showed many fine keratic precipitates, 3+ aqueous cells, 1+aqueous flare, a pale yellow retinal exudate in the nasosuperior periphery, three isolated degenerative areas in the temporosuperior, temporoinferior, and inferior periphery, and periphlebitis in the temporosuperior and nasoinferior midperiphery. The left eye was unremarkable except for faint retinal degeneration in the nasosuperior and temporoinferior periphery and a pigmented degenerative area in the superior midperiphery. Oral betamethasone (3 mg) was started and then gradually tapered. The exudate resulted in localized retinochoroidal degeneration.

Results

Antibody titers in the serum and aqueous humor to varicella-zoster, herpes simplex type 1, and Epstein-Barr virus were determined by indirect fluorescent antibody techniques. Briefly, 100 μl of the sample (serum or aqueous humor) was mixed with 0.9 ml of phosphate-buffered saline and inactivated at 56 C for 30 minutes. The dilution series was added to the smear of virus-infected cells and incubated at 4 C overnight. After extensive washing, fluorescein isothiocyanate-conjugated anti-human-IgG antibody was added, incubated at 37 C for

30 minutes, and washed. The smear was then examined with fluorescent microscopy and the titer was described as maximum dilution folds to show positive fluorescence.

IgG antibody titers in the serum to varicella-zoster virus, herpes simplex virus type 1, and Epstein-Barr virus (viral capsid antigen, nuclear antigen, early antigen) were determined in both acute and convalescent phases of all six cases. No significant increases in the titers were observed.

The IgG antibody titers in the aqueous humor were determined only for varicella-zoster virus and herpes simplex virus type 1 in three of the cases (Table). Only the left eye in Case 1 showed significant rise of the titer for varicella-zoster virus. Case 3 showed a rise of the convalescent titer for varicella-zoster virus. The significance of this finding is unclear since the acute phase titer was not determined. In Case 4 both eyes showed the rise for varicella-zoster virus but no significant change between the aqueous titers of the acute and convalescent phases. Ideally, aqueous titers should be correlated with aqueous immunoglobulin levels,[8] which were not determined in our cases.

Discussion

All six patients showed peripheral to midperipheral pale yellow retinal exudates, although differing in severity, which were typical of those described previously in acute retinal necrosis syndrome. The fundus changes were associated with vitreous opacities and anterior uveitis. These factors led us to the diagnosis of acute retinal necrosis syndrome. The exudates remained stationary or extended gradually to the posterior pole and resulted in localized retinochoroidal degeneration before becoming confluent at 360 degrees (Fig. 4).

We suggest that this mild, self-limiting course is one of the natural developments of acute retinal necrosis syndrome although somewhat modified by therapy such as antivirals, corticosteroids, or both. Some researchers may believe that such a mild type should not be included in acute retinal necrosis syndrome or that it was the result of treatment. We, however, propose that acute retinal necrosis syndrome has varying degrees of severity from mild to fulminant. The retinal exudates appeared to be the same as those described previously, and varicella-zoster virus was believed to be a causative agent based on the increased titers to the virus in the aqueous humor of three of the patients examined. One alternative is that these cases should not be included in acute retinal necrosis syndrome, although their initial lesions simulate those in acute retinal necrosis syndrome, and that they represent a new disease entity. Differential diagnosis may include multifocal chorioretinitis, caused by Epstein-Barr virus.[9] However, Epstein-Barr virus does not show confluent lesions as were present in our cases.

All six patients received a large dose of corticosteroid combined with acyclovir, although in low doses in four patients and plasma exchange

TABLE
ANTIBODY TITERS IN AQUEOUS HUMOR TO HERPES VIRUS GROUP*

CASE NO.	EYE	ACUTE PHASE† HERPES SIMPLEX TYPE 1	ACUTE PHASE† VARICELLA-ZOSTER VIRUS	CONVALESCENT PHASE† HERPES SIMPLEX TYPE 1	CONVALESCENT PHASE† VARICELLA-ZOSTER VIRUS
1	R.E.	—	—	—	—
	L.E.	10	10	10	80
2	L.E.	—	—	—	—
3	L.E.	—	—	10	160
4	R.E.	10	80	10	40
	L.E.	10	40	10	20
5	L.E.	—	—	—	—
6	R.E.	—	—	—	—

*Antibody titers were determined by fluorescent antibody technique.

†— indicates not determined.

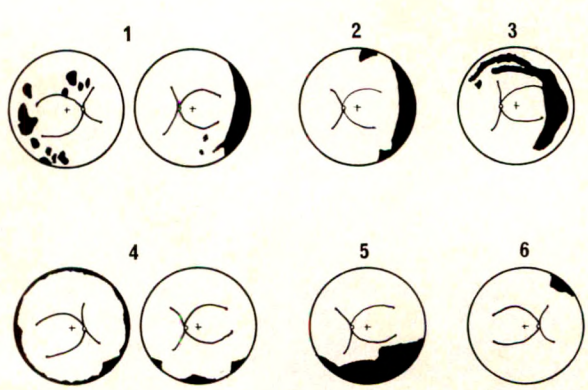


Fig. 4 (Matsuo and associates). Schematic drawings of the areas of the retina involved in six cases.

in one. The mild course could thus be attributed to the treatment. But we believe it to be one of the natural courses of acute retinal necrosis syndrome, because the exudates extended gradually and did not become confluent. The exudates in typical acute retinal necrosis syndrome, including our cases, extend rapidly to the posterior pole and to the whole meridian despite the administration of corticosteroids and acyclovir.[10]

We propose that acute retinal necrosis syndrome consists of a varying spectrum of severity from mild to fulminant depending on the speed (rapid or gradual) of the growth of the retinal exudates and the area (wide or limited) of the involved retina. In the fulminant type, the wide area of the retina quickly becomes necrotic and the vitreous is severely inflamed, which enhances formation of retinal tears and vitreoretinal adhesions. The tears lead to rhegmatogenous retinal detachment and the adhesions to traction retinal detachment when the inflamed vitreous contracts. In the mild type, the area of necrotic retina is limited and the vitreous is moderately inflamed, leading to reduced vitreoretinal complications. In Cases 3 and 5, which had relatively wider areas of the retina involved than in the other cases, the prognosis still was good. The patients were both old and the fellow eyes in each showed complete posterior vitreous detachment. Presumed formation of complete posterior vitreous detachment before the involvement of acute retinal necrosis syndrome, which would reduce the vitreoretinal traction, may thus have played a role in their successful outcome. We believe it necessary to administer corticosteroids in this mild type of acute retinal necrosis syndrome because corticosteroids may decrease vitreous opacities and anterior uveitis, and reduce the rate of late vitreoretinal and anterior segment complications. The effect of acyclovir on acute retinal necrosis syndrome, including the mild type, is presently unknown.

The concept that acute retinal necrosis syndrome has varying degrees from mild to fulminant course is particularly important to evaluate the effect of various modes of treatment. Until now, the therapeutic effects of reattachment surgery,[11] photocoagulation,[12] and administration of acyclovir[13] on acute retinal necrosis syndrome have been reported. The results must be reviewed in light of possible varying degrees of acute retinal necrosis syndrome, as demonstrated in our six cases. The increased rate of the mild type of acute retinal necrosis syndrome in our institutions can be attributed to the awareness of acute retinal necrosis syndrome, which prompted us to examine peripheral fundus with mydriasis.

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Asymmetric Retinopathy in Patients With Diabetes Mellitus

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We reviewed retrospectively the records of 57 diabetic patients with asymmetric retinopathy persisting for two years or more (mean, 4.8 years) to identify intraocular risk and protective factors for the development of proliferative retinopathy. For each patient in this series, the more severely affected eye had proliferative retinopathy and the fellow eye had either background diabetic retinopathy or no retinopathy. Branch vein occlusion (P = .016) was identified as a statistically significant risk factor for proliferative retinopathy and chorioretinal scarring (P = .031) was found to be a statistically significant protective intraocular factor. In 34 patients with long-standing asymmetric retinopathy, no intraocular risk or protective factors were identified.

DIABETES MELLITUS is a systemic disease in which retinopathy usually develops in a symmetric pattern over a long period of time. Aiello and associates[1] observed that eyes with extensive chorioretinal scarring were often protected from more severe retinopathy. Wessing and Meyer-Schwickerath[2] induced chorioretinal scarring by xenon arc photocoagulation and found similar results. Identification of other protective or exacerbating intraocular factors may be important in planning new approaches to treatment. We reviewed this series of patients with maintained asymmetric retinopathy to identify clinically important intraocular risk and protective factors.

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Patients and Methods

Asymmetric retinopathy was defined in this retrospective review as proliferative retinopathy in one eye and background or no diabetic retinopathy in the fellow eye persisting for at least two years. The patient population included all diabetic patients examined during 1970 through 1983 who met this requirement. We reviewed the medical records, and the photographic files when available, on each patient. Many patients did not have fundus photographs available for independent comparison. Patients were excluded when vitreous hemorrhage or other media opacity prevented definite identification of neovascularization. Patients who received laser treatment before the first identification of asymmetric retinopathy were excluded, since laser treatment itself can retard the progression of retinopathy. If patients received any laser treatment to the eye with background or no diabetic retinopathy during the two-year minimum follow-up period (for example, focal treatment for diabetic macular edema), these patients were also excluded.

After these exclusion criteria were met, the charts of 57 patients were available for review in this study. Follow-up information was gathered from the latest examination by the authors or by communication with the referring ophthalmologist. There were 30 men and 27 women who ranged in age from 21 to 79 years (mean, 57.8 years). The duration of diabetes mellitus reported in the patient's history ranged from one to 65 years (mean, 20.2 years). The duration of asymmetric retinopathy ranged from 2.0 to 14.4 years (mean, 4.8 years). Proliferative diabetic retinopathy occurred in 30 right eyes and 27 left eyes in this study population.

Multiple intraocular characteristics of these patients were entered into suitable forms for computer analysis (Table). Factors examined were derived from reviewing the literature on asymmetric diabetic retinopathy. We have divided these factors into those previously re-

TABLE
DISTRIBUTION OF OCULAR FACTORS BETWEEN EYES WITH BACKGROUND DIABETIC RETINOPATHY AND PROLIFERATIVE RETINOPATHY (N = 57)

STUDY FACTORS HYPOTHESIZED TO AFFECT RISK OF PROLIFERATIVE RETINOPATHY	NO. OF EYES WITH BACKGROUND OR NO RETINOPATHY	NO. OF EYES WITH PROLIFERATIVE RETINOPATHY	P VALUE*
Increase risk			
Branch vein occlusion	0	7	.016
Previous extracapsular cataract extraction	3	0	.250
Previous intracapsular cataract extraction	7	7	1.000
Vitreous loss	0	3	—†
Trauma, radiation, uveitis, or tumor	0	0	—
Decrease risk			
Chorioretinal scarring	6	0	.031
Optic atrophy	4	0	.125
Retinal pigment epithelial atrophy	3	0	.250
Complete vitreous detachment	13	9	.388
Amblyopia	2	0	.500
Ipsilateral carotid artery obstructive disease	1	0	1.000

*P value according to McNemar's test for paired data.

†Vitreous loss during previous cataract surgery occurred in none of ten eyes with background or no retinopathy in contrast to three of seven eyes with proliferative retinopathy (P = .102 by chi square).

ported to favor proliferative retinopathy and those previously reported to protect against proliferative retinopathy. Statistical analysis was performed by using Student's *t*-test for continuous data and McNemar's test for paired data for contingency tables. $P < .05$ was considered statistically significant.

Results

Two study factors showed an influence on the development of proliferative retinopathy and reached statistical significance (Table). Branch vein occlusion occurred in seven eyes with proliferative retinopathy but in no eyes with background or no diabetic retinopathy (P = .016). Extensive long-standing chorioretinal scarring was present in six eyes with background or no diabetic retinopathy but in no eyes with proliferative diabetic retinopathy (P = .031).

None of the other factors studied showed a statistically significant imbalance between proliferative retinopathy and background or no diabetic retinopathy eyes, although certain trends were suggested (Table). Optic atrophy (Figs. 1 and 2), retinal pigment epithelial atrophy, and amblyopia showed trends of being a protective influence; these factors were seen in four, three, and two eyes with background or no diabetic retinopathy, respectively, but in no eyes with proliferative retinopathy.

Complete posterior vitreous detachment was described in 13 eyes with background diabetic retinopathy and nine eyes with proliferative retinopathy. The status of the vitreous was not recorded in the chart or available on follow-up examination reports in 29 eyes with background diabetic retinopathy and 34 eyes with proliferative retinopathy.

Uncomplicated intracapsular cataract surgery was previously performed in 14 eyes and was equally distributed between proliferative retinopathy and background retinopathy groups. By contrast, uncomplicated extracapsular cataract surgery was previously performed in three eyes, all of which had background retinopathy. Vitreous loss during cataract surgery occurred in three eyes with proliferative retinopathy but in no eyes with background diabetic retinopathy.

The mean spherical equivalent refractive error was +0.3 diopters in eyes with proliferative retinopathy and +0.1 diopters in eyes with background or no diabetic retinopathy. There were four patients in whom there was a greater

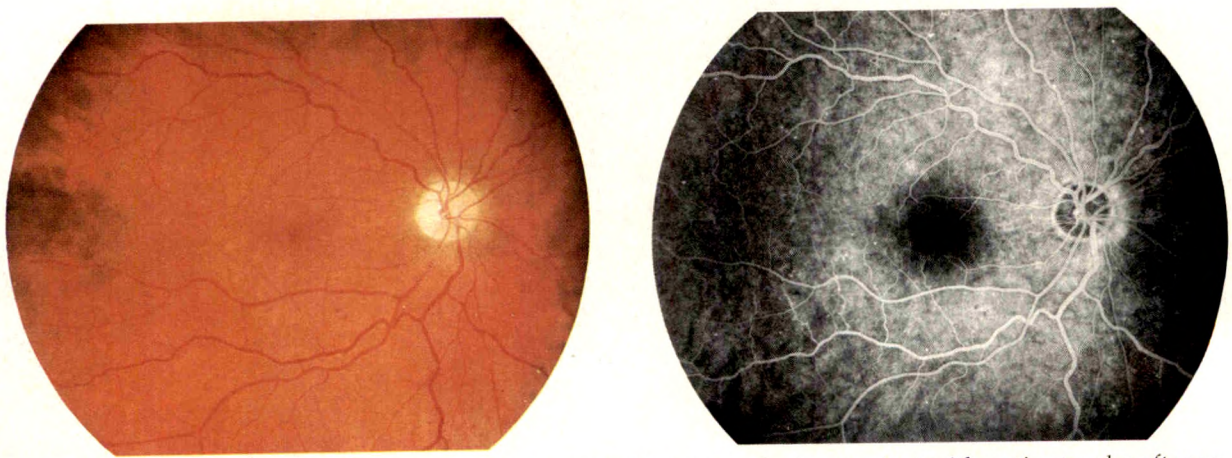


Fig. 1 (Browning, Flynn, and Blankenship). Asymmetric retinopathy in a patient with optic atrophy after an episode of optic neuritis in the right eye. Left, Fundus photograph shows minimal background diabetic retinopathy consisting of isolated microaneurysms and pallor of the optic nerve head. Right, Fluorescein angiogram demonstrates minimal diabetic capillary disease and confirms the presence of a limited number of microaneurysms. After two years of follow-up, the right eye has shown slight progression of background diabetic retinopathy, but visual acuity remains 20/25.

than 1-diopter anisometropia (2.3 diopters was the largest difference in refractive errors between eyes). In three of these four patients, the more myopic eye had proliferative retinopathy.

The mean intraocular pressure was 16.4 mm Hg in eyes with proliferative retinopathy and 16.7 mm Hg in eyes with background or no diabetic retinopathy. Eight patients had intraocular pressure differences of 3 mm Hg or more at the initial visit. The lower intraocular pressure was found in the eye with proliferative retinopathy in six patients and the eye with background or no diabetic retinopathy in two patients. These differences were not statistically significant.

Five patients had no retinopathy in one eye and proliferative retinopathy in the fellow eye. Three of these patients had two protective factors present in the eye with no retinopathy, including both optic atrophy and chorioretinal

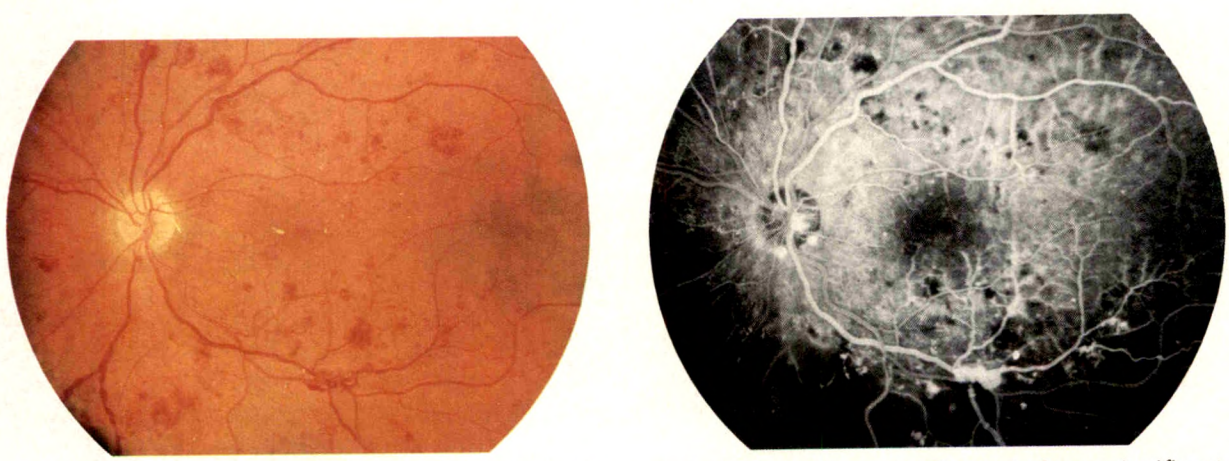


Fig. 2 (Browning, Flynn, and Blankenship). Left eye of the patient shown in Figure 1 shows significant proliferative retinopathy. Left, Fundus photograph shows moderate neovascularization elsewhere and mild neovascularization of the disk. Right, Fluorescein angiogram demonstrates marked capillary nonperfusion and confirms the characteristic leakage features of neovascularization. Initial visual acuity was 20/25. Despite prompt panretinal photocoagulation, this eye developed a nonclearing vitreous hemorrhage. Following pars plana vitrectomy and laser panretinal photocoagulation, visual acuity is 20/200 after two years of follow-up.

scarring in two patients and both macular retinal pigment epithelial atrophy and chorioretinal scarring in another patient. One patient in this group had one eye with an anterior chamber intraocular lens and a history of vitreous loss at cataract surgery; this eye developed proliferative retinopathy. The final patient in this group had no identifiable risk or protective factors. Fluorescein angiography was not performed to evaluate the possibility of subtle angiographic changes in the eye with no ophthalmoscopically visible changes.

Discussion

Many diabetic patients develop neovascularization in one eye shortly before the onset of proliferative disease in the fellow eye. By requiring at least two years of asymmetry and by eliminating any treatment influences on this patient population, we excluded short-term asymmetry and identified a patient population in which we expected intraocular protective or risk factors for proliferation to be operating.

This retrospective study differs from previous similar reports because of its inclusion and exclusion criteria. Valone, McMeel, and Franks[3,4] reported a series of 136 diabetic patients with asymmetric retinopathy who were followed up for at least three months. This short period of required asymmetry would not be adequate for evaluation of selected intraocular factors. Valone, McMeel, and Franks did not study risk factors such as amblyopia, optic atrophy, vitreous loss at cataract surgery, but did study posterior vitreous detachment, chorioretinal scarring, and intraocular pressure determination.

Two local factors in the current series reached statistical significance, including branch vein occlusion ($P = .016$) as an important intraocular risk factor and chorioretinal scarring ($P = .031$) as a protective factor against proliferative diabetic retinopathy. Long-term follow-up of eyes with branch vein occlusion with large areas of nonperfusion has been reported to include the development of neovascularization in 36% of eyes.[5] The mechanism of neovascularization in branch vein occlusion is similar to proposed mechanisms for proliferative diabetic retinopathy.[6] In Valone, McMeel, and Franks' series,[3] 12 patients had proliferative retinopathy in one eye and no visible diabetic retinopathy in the fellow eye. In six of these patients, branch vein occlusion was the presumed cause of proliferative retinopathy; in one patient, a macular chorioretinal scar was present in the eye with no retinopathy; in the remaining five patients, no intraocular factors were present to explain the asymmetry. This distribution of intraocular factors in their series is similar to the present series.

The protective influence of chorioretinal scarring has been documented,[1,2] although the exact mechanism for this influence is debated. The loss of retinal ganglion cells together with optic atrophy may reduce the metabolic requirements in such eyes and secondarily reduce the ischemic stimulus for neovascularization.[7,8] This reduction in retinal oxygenation requirements has been a proposed mechanism for the beneficial effects of panretinal photocoagulation treatment in proliferative diabetic retinopathy.[9,10]

Although these factors do not reach statistical significance, trends suggest that retinal pigment epithelial atrophy in the macula is a protective influence while vitreous loss from complicated cataract surgery is an exacerbating intraocular influence. As previously discussed, atrophic macular disease may be associated with a corresponding loss of retinal ganglion cells and may reduce retinal oxygen demand.[7] Vitreous loss may have an adverse effect by increasing intraocular inflammation or by increasing vitreoretinal traction.

Moderate ipsilateral carotid obstructive disease has previously been associated with protection from proliferative diabetic retinopathy.[11,12] The protective effect of ipsilateral carotid occlusive disease has been speculated to be a result of reduction in retinal arterial perfusion pressure.[11] Conversely, the ocular ischemic syndrome occurs in the eye with 90% or more occlusion of the ipsilateral common carotid artery and may be associated with retinal and iris neovascularization.[12] Only one patient in our series had documented unilateral carotid vascular disease, and this patient showed background diabetic retinopathy on the involved side.

Amblyopia has been considered to be a protective influence against proliferative diabetic retinopathy by many clinicians, although there is no evidence in the literature to document this observation. Data obtained by Grunwald and associates[13] suggest a decrease in retinal blood flow to amblyopic eyes. The decrease in retinal oxygen demand by amblyopic eyes, therefore, might protect these eyes from developing neo-

vascularization. Our data support this impression, but the number of patients is too small to reach statistical significance.

The importance of vitreoretinal traction in proliferative retinopathy was described by Davis.[14] Two clinical series[15,16] demonstrated that complete posterior vitreous detachment protects against development of proliferative retinopathy. Our study supports this conclusion, but the incomplete data regarding the vitreous status of our patients make further statistical evaluation impossible.

We found no association between uncomplicated aphakia and protection from or increased risk for proliferative retinopathy. In Valone, McMeel, and Franks' study,[3] five patients had unilateral aphakia and in four of the five, the aphakic eye had proliferative retinopathy. The distribution of findings in these patients conflicts with our results and suggests but does not prove an exacerbating role for cataract extraction.

Becker[17] showed that intraocular pressures over 23 mm Hg were observed in 3% of eyes with proliferative retinopathy but 9% of eyes with background diabetic retinopathy, suggesting a protective influence of high intraocular pressure. An earlier study by Becker and associates[18] showed a slowed progression of retinopathy by raising intraocular pressure using topical corticosteroids in five of ten patients who began the study with symmetric retinopathy. Similar observations on reduced retinopathy in eyes with increased intraocular pressure have been made by others.[17-21] Valone, McMeel, and Franks[3] studied patients without iris neovascularization having pressure differences of 3 mm Hg or more between the eyes. In 41 such patients (20%), the eyes with background diabetic retinopathy had higher intraocular pressure, but in 25 patients (12%), the eyes with proliferative retinopathy had a higher intraocular pressure. Of eight patients without rubeosis iridis in our study meeting these criteria, the intraocular pressure was higher in the eye with background diabetic retinopathy in six patients and higher in the eye with proliferative retinopathy in two patients. A protective effect of higher intraocular pressure is suggested, but the small number of patients in each group fails to reach statistical significance.

In this study, anisometropia greater than 1 diopter occurred in only four patients, but in three of them, the more myopic eye had background diabetic retinopathy. In Valone, McMeel, and Franks' study,[4] there were ten patients with anisometropia of 1 diopter or more, and in six, the more myopic eye had background diabetic retinopathy. None of these eyes showed high degrees of anisometropia. Therefore, no test was possible of Jain, Luthra, and Das' hypothesis[22] that myopia of 5 diopters or more protects against proliferative diabetic retinopathy. Rand and associates[23] and Baker and associates[24] reported data suggesting that myopia reduces severity of retinopathy only in HLA-DR phenotypes 4/0, 3/0, and X/X. No HLA-DR phenotyping was performed in our patients.

In four of the five patients with no retinopathy in one eye and proliferative retinopathy in the fellow eye, one or more identifiable risk or protective factors were present. Of particular interest were three patients in this group in whom two protective factors were present in the eye with no retinopathy (chorioretinal scarring with either optic atrophy or macular retinal pigment epithelial atrophy). Only one of the five patients in this group had no identifiable ocular factors to account for the asymmetry.

The effects of unilateral radiation, trauma, uveitis, and tumors on proliferative retinopathy cannot be evaluated in this study since no patient had any of these coincident conditions. The lack of any of the studied factors in 34 patients with long-standing asymmetric retinopathy suggests that other unrecognized factors may exist.

Several study factors (for example, optic atrophy) approached, but did not reach, statistical significance. A larger study might have demonstrated statistical significance of one or more factors that failed to reach that level in our study.

This study suffers from the problems inherent in all retrospective studies. A full description of all study factors was not available in some patients and the overall number of positive factors was small. Many of the study factors analyzed are well known to ophthalmologists as they examine patients with asymmetric retinopathy. This awareness may have biased the results such that well-known risk and protective factors were identified and recorded more often than less well-known unsuspected factors. This bias could skew the distribution of influencing factors away from the true distribution. Until prospective data on each of these influencing factors are available, the results reported here may serve as a guide for the clinician regarding the origin of asymmetric

retinopathy in diabetic patients and may influence the timing of photocoagulation for the second eye in such cases. We emphasize the need for further investigation in identifying unknown intraocular factors accounting for over half of all patients in this series with asymmetric retinopathy.

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Detection of the Carrier State of X-Linked Retinoschisis

Geoffry B. Arden, M.D., Michael B. Gorin, M.D., Philip J. Polkinghorne, M.D., Marcelle Jay, Ph.D., and Alan C. Bird, M.D.

We determined the extent of suppressive rod-cone interaction in 11 obligate carriers and eight potential carriers of X-linked retinoschisis from eight families. Despite otherwise normal ophthalmoscopic and functional testing, all of the obligate heterozygous carriers demonstrated a complete absence of normal rod-cone interaction. Of the potential heterozygous carriers, three had normal rod-cone interactions, two had no detectable interaction, and two yielded technically unsatisfactory results. This lack of rod-cone interactions allows heterozygous individuals to be identified clinically and has implications concerning the origin of this inherited disorder.

JUVENILE RETINOSCHISIS, first described by Haas in 1898,[1] was recognized as an X-linked disorder in 1913.[2] Since that time there have been numerous accounts of the fundus appearance,[3] electrophysiologic responses,[4] and natural course of this condition.[5] Abnormalities of the retina have been noted in patients as young as 3 months of age and are probably present from birth. Virtually all affected males demonstrate foveal retinoschisis, with up to 50% of these individuals having bilateral peripheral retinoschisis. Abnormalities of the retinal vasculature, pigment epithelium, and vitreous have also been commonly noted.[3] Visual acuity is variably affected early in the disease, and generally there is a slow deterioration that occurs throughout life, with the adult affected male usually achieving a visual acuity of only 20/200. Mild dyschromatopsia is common and all affected individuals demonstrate an abnormal electroretinogram, with loss of the b-wave and retention of the normal a-wave.[4] This suggests that Müller cells may play a significant role in this disorder.[6] Histopathologic findings of eyes from patients with X-linked retinoschisis also support this view.[7]

Unlike in other ocular X-linked recessive disorders, no abnormalities have been consistently reported in heterozygous carriers of X-linked retinoschisis.[3] Ocular albinism, choroideremia, and X-linked retinitis pigmentosa manifest varying degrees of disturbance of retinal appearance and function consistent with the Lyon hypothesis of X-chromosomal inactivation.[8]

Herein we report a new approach that appears to distinguish X-linked retinoschisis carriers from normal individuals. In 1983, Goldberg, Frumkes, and Nygaard[9] described a form of suppressive rod-cone interaction. The ability of the photopic system to detect flicker became impaired as rods dark adapted; conversely, if dark-adapted rods were exposed to dim light this function improved. The action spectrum of the light that improved cone flicker corresponded to the rhodopsin absorption spectrum.[10,11] Arden[12] showed that dark-adapted rods imposed a low-pass filter on the cone system. Recent experiments[13] have shown that a phenomenon analogous to suppressive rod-cone interaction can be observed in the electroretinograms of humans and animals, and also by single-cell recording in the horizontal cells of lower vertebrates.[14] A nonlinear relationship between rod membrane potential and rod synaptic signal strength[15] has been reported, which could explain how the time course of the modulation of cone thresholds parallels rod thresholds during dark adaptation.[16]

The rod-cone interaction is probably a result of postsynaptic feedback, possibly from horizontal cells, onto cone photoreceptors. In conditions in which only the photoreceptors were diseased, rod-cone interaction can be demonstrated.[17,18] By contrast, this effect was absent in patients with X-linked stationary night blindness and, more particularly, X-linked retino-

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From the Institute of Ophthalmology, University of London, and the Retinal Diagnostic (Dr. Bird) and the Electrodiagnostic (Dr. Arden) Departments of Moorfields Eye Hospital, London, England. This study was supported in part by Medical Research Council grant 8425012 and National Eye Institute grant 1 R01 EY05 984 01A1 (Dr. Arden). Dr. Gorin received a 1986 fellowship from the Retinitis Pigmentosa Foundation.

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schisis, conditions in which postsynaptic abnormalities appear to be the primary disturbance. The recent in vitro work implicating the Müller cell as a migration determinant for retinal development and neuronal interconnections[19] would explain the absence of this phenomenon in X-linked retinoschisis, which is thought to be a primary Müller cell disease. This suggests that a test based on this phenomenon might be able to detect the earliest stages of retinal disease.

In an initial examination of the rod-cone interaction in six obligate carriers from a single kindred, we found that the alteration of cone flicker threshold by rod backgrounds was completely abolished. Based on these results, we extended our studies to include a number of obligate and possible carriers of X-linked retinoschisis from this and other families.

Subjects and Methods

Patients—Families with X-linked retinoschisis were identified from the Moorfields Genetic Clinic. The original diagnosis was based on clinical examination, the characteristic electroretinogram abnormalities, and family history. Women who were either obligate heterozygotes or had a 50% risk of being heterozygous were contacted. The test subject population consisted of 19 women who ranged in age from 18 to 65 years. All were healthy, and none had visual complaints or a history of ocular disorders. Best corrected visual acuity was 20/25 or better and results of clinical examinations of the anterior segment and fundus were unremarkable. The initial six obligate and four potential heterozygous women were identified from the pedigree shown in Figure 1, left. The remaining five obligate and four potential heterozygous women were selected from seven unrelated families (Fig. 1, right). The nature of the study was explained fully before obtaining informed consent.

Clinical examinations—Every participant was evaluated by assessment of visual acuity, indirect ophthalmoscopy and fundus photography, and pattern electroretinography.

Measurement of rod-cone interaction—The right pupil was dilated with 1% tropicamide and patched with an opaque pad for dark adaptation for 45 minutes. The test was performed in a darkened room. The patient was positioned in a modified Lister perimeter, the target of which had been replaced by an arrangement of light-emitting diodes.[17,20] Patients who wore glasses retained them. An area 10 degrees nasal to fixation on the horizontal meridian was tested. Fixation was maintained on a dim red, light-emitting diode target. The absolute rod threshold for the test location was determined by using a 5-degree target, rear illuminated by nine blue light-emitting diodes.

Next, we determined the minimum light intensity required for the subject to perceive the flicker in a 30-minute target formed by a single red light-emitting diode in the center of the test area. The output was 100% modulated at 15 Hz. With mean intensities close to the cone threshold, the stimulus appears continuous, but as the intensity increases, the subject can discriminate the rapid alternation of light and darkness. The target intensity at which the patient can first detect the flickering of the red light is

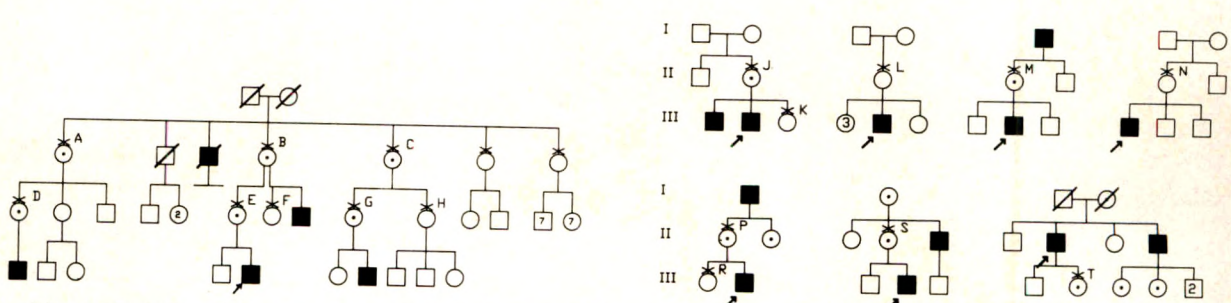


Fig. 1 (Arden and associates). Left, Pedigree of the primary X-linked retinoschisis family. The symbols conform to the standard conventions: male, square; female, circle; deceased, /; affected, shaded; normal or unknown, open; obligate carrier, central dot; and examined, X. The arrow indicates the proband for whom the diagnosis was confirmed. The letters assigned to the tested individuals correspond to the labeling of the results shown in Figures 3 and 4. Right, Pedigrees of other families with X-linked retinoschisis investigated in this study.

the flicker threshold. Untrained subjects have considerable difficulty in consistently reporting the onset of flicker for a nonfoveal test site. The longest part of the testing session was the training period, during which the red light was repeatedly presented. In some cases in which flicker thresholds seemed extremely high, the 660-nm light used to stimulate cones might have also stimulated the rod system. For this reason, exposure to the red light was reduced as much as possible. After an approximate flicker threshold had been determined, intensity controls were adjusted so that when a flickering light of progressively increasing intensity was shown, it increased from 0 to threshold in four to eight seconds. When the patient responded, the light was extinguished, and the patient remained in darkness for at least 15 seconds before beginning another trial. In the session proper, three or more trials were recorded; the intensity of the blue background light-emitting diodes was then modified, and another set of thresholds were determined. In all cases, the intensity was altered in a random manner, and when all the intensity levels had been displayed, the tests were repeated in reverse order. In some patients there was an indication of improvement of threshold during the session (a training effect), while others showed a small progressive increase in threshold (fatigue). The test lasted between 45 minutes and 1½ hours. The experimenter altered the red flickering test light manually by turning a ten-turn potentiometer. During the test session the reading on the potentiometer was not visible. The examiner intentionally varied the rate of change of the target intensity to ensure that patients were not responding to a fixed time interval after the red light intensity began to increase.

Results

Rod-cone interactions—All test subjects were examined by one of us (G.B.A.). The initial six subjects were known to be obligate carriers, but for the remaining obligate and potential carriers, the examiner was masked to their genetic status in order to minimize observer bias.

The rod threshold at 10 degrees nasal to fixation varied from 8.1×10^{-7} to 9.7×10^{-6} and were in the normal range for this laboratory. In normal subjects (Fig. 2), the cone flicker threshold was constant for backgrounds between −0.5 and +1.0 log unit above absolute rod threshold. As the intensity of the blue background increased, the cone flicker threshold decreased about 0.5 log unit. With further increases of the background intensity, the blue light became suprathreshold for the cone system, and the flicker threshold rose as expected with increment thresholds. These results are similar to those reported previously.[17]

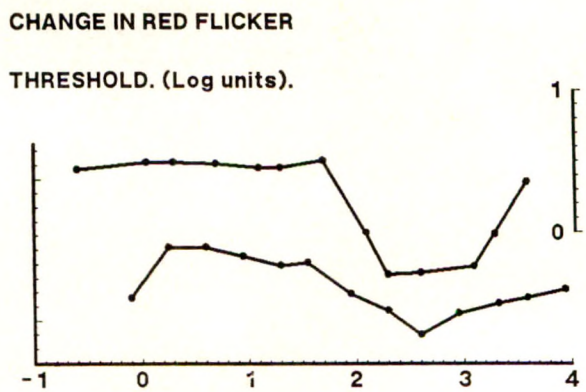


Fig. 2 (Arden and associates). The rod-cone interaction of two normal subjects. The cone flicker threshold (ordinate) is plotted against the intensity of the blue light background (abscissa). Note the decrease in the threshold of the cone flicker threshold as the intensity of the rod stimulation by blue background is increased.

Because of the technique of measurement and training, the precision of flicker threshold determination is high. However, the thresholds in our subjects varied considerably. Ranging from 0.008 to 1.8 cd/m^2, these values reflect the variability of the criterion that each patient established for recognizing flicker. This variability is seen in normal subjects and reflects the complexity of the ocular and higher central nervous system processing that must be involved for each patient. In two instances, the test was not carried out in a satisfactory manner so that thresholds apparently rose and fell randomly with respect to the blue background intensity. These two subjects (both sisters and potential heterozygous carriers of X-linked retinoschisis) could not differentiate between the absolute and flicker cone threshold. The remaining 17 patients were able to maintain consistency and reproducibility among multiple trials. There was no relationship between the actual cone flicker thresholds and patient age, carrier status, rod threshold, or rod-cone response.

None of the 11 obligate heterozygous individuals demonstrated any evidence of a rod-cone interaction (Fig. 3). The variation of the mean level of background intensity that was suprathreshold for the cone system was only 0.03 log unit. For clarity in exposition, the ordinate is shown in terms of logarithmic multiples of cone threshold and the results of successive patients are displaced downward by 0.5 log unit to separate the graphs. This small level of variation reflects the internal consistency of the subjects and the experimental paradigm. Two distinct types of responses were observed in the potential heterozygous women (Fig. 4). Three demonstrated a change in cone flicker threshold in response to changing rod stimulation similar to the normals, while two failed to show any rod-cone interaction.

Discussion

For the first time, we detected a consistent disturbance of retinal function in women heterozygous for X-linked retinoschisis. The presence of normal rod-cone responses in other family members, and the appropriate segregation of normal and abnormal responses among those at 50% risk of being heterozygous, indicate, but do not prove, that this abnormality of rod-cone interaction is associated with the gene for X-linked retinoschisis. A considerably larger number of subjects and prospective testing will be necessary to establish the validity and accuracy of the rod-cone interaction as an indicator of carrier status for genetic counseling purposes. However, our results raise the possibility of carrier ascertainment for a large number of individuals at risk who may not be informative by current linkage analysis. For example, in a DNA linkage analysis on the family shown in Figure 1, left, none of the current markers are informative so that non-obligate heterozygous carriers cannot be identified. The ability to test an individual at risk of having the X-linked retinoschisis gene independently of the pedigree or available family members would be an invaluable clinical tool.

There are a number of strategies that have been used for measuring rod-cone interactions. Paradigms using varying background sizes and target sizes as well as electroretinograms to assess rod-cone interactions have been

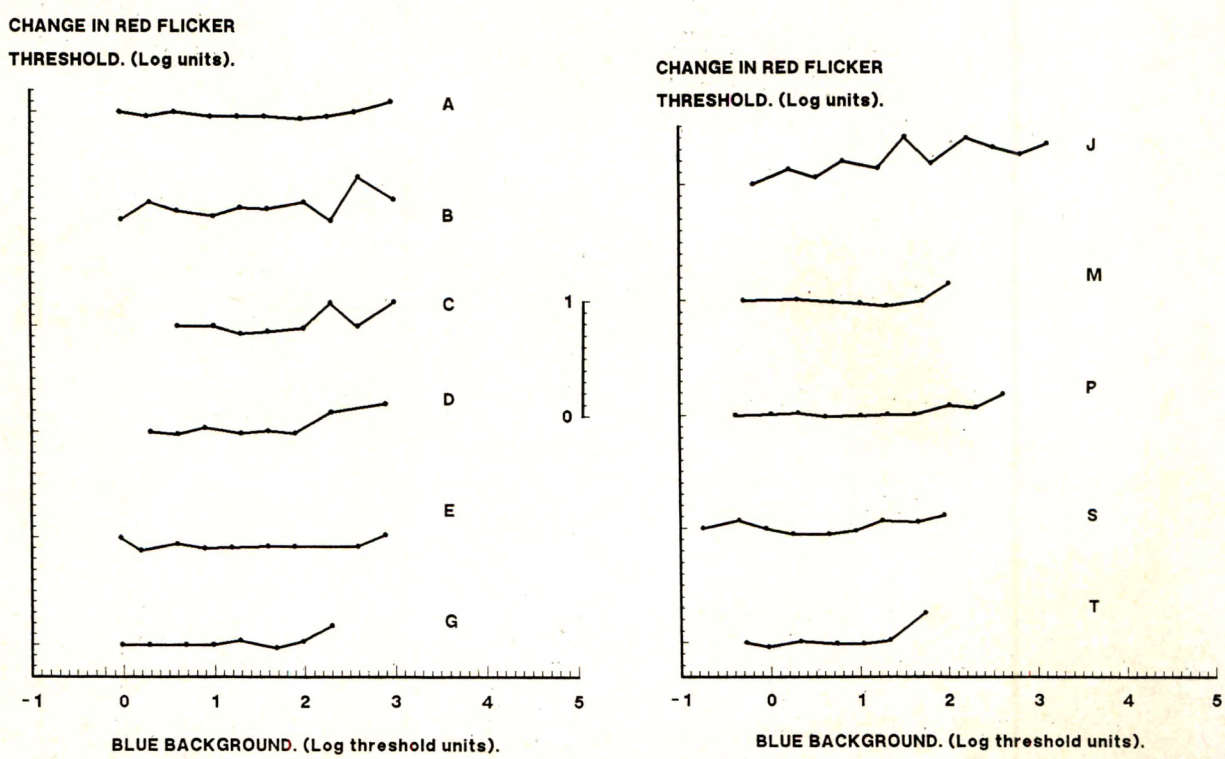


Fig. 3 (Arden and associates). The rod-cone interactions of the 11 obligate carriers of X-linked retinoschisis. The ordinate and abscissa correspond to those of Figure 2.

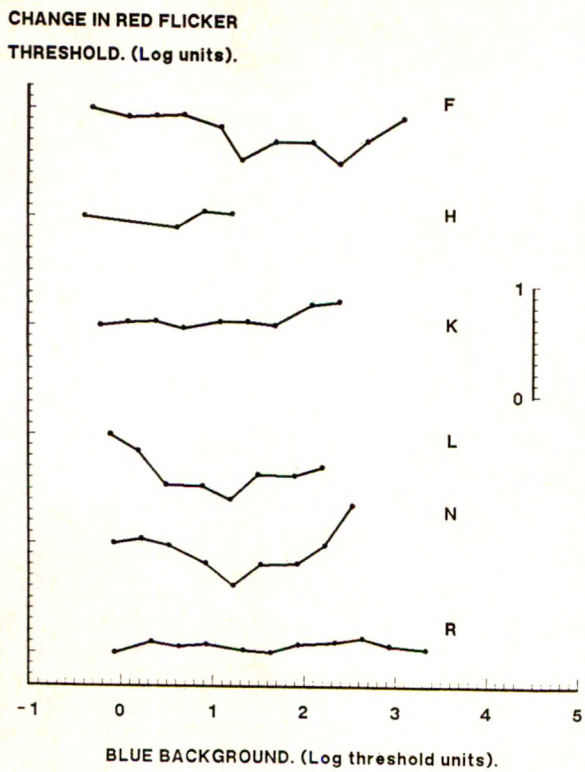


Fig. 4 (Arden and associates). The rod-cone interactions of the potential carriers of X-linked retinoschisis. The results from the two potential carriers (sisters) who gave technically inconsistent results have been omitted. The ordinate and abscissa correspond to those of Figure 2.

used.[13,21] The topography of the response in the retina has also been evaluated.[22] Our testing strategy is based on the experience and equipment that has been developed at this institution. By selecting a constant angle nasal to fixation, and using the current background and target illumination systems, we could readily compare the responses of these test subjects to results from other patients and normal volunteers.

In contrast to published work from this laboratory,[17,18] Alexander and Fishman[23] reported normal alterations in the cone flicker threshold in the light- vs dark-adapted states for a single patient with X-linked retinoschisis and a patient with congenital stationary night blindness. While they may have been examining a different subset of patients from our population, these conflicting responses may reflect a critical difference in the testing methods used. In our method, we examine the relationship of cone flicker threshold to changing background intensities at a single retinal site, while Alexander and Fishman evaluate the regional differences in cone flicker threshold in either the dark-adapted or light-adapted state over a range of retinal loci.

It is striking that rod-cone interaction is absent in carriers of X-linked retinoschisis. In other retinal disorders such as choroideremia and X-linked retinitis pigmentosa, the mosaicism generated by random inactivation of the normal X-chromosome in carriers gives rise to a variable abnormality detected either by clinical appearance or by a variety of tests. Some heterozygous individuals may exhibit minimal evidence of the abnormal gene, while others may be affected to such an extent as to have significant visual impairment.

With the current size of our subject population we cannot exclude the possibility that variations in rod-cone interaction may occur in other carriers of retinoschisis. Given the present evidence, however, it is also reasonable to consider mechanisms by which a global perturbation of neuronal interaction can be generated by partial gene expression. The formation of the interneuronal connections responsible for the observed rod-cone interaction probably occurs during retinal development, perhaps under Müller cell influence. A Müller cell-derived diffusable factor that may be essential for retinal structure[24,25] could be affected by the retinoschisis allele leading to a panretinal disturbance of development. Alternatively, a continuous syncytium of horizontal cells may be required before the rod-cone interaction can develop, and even a partial expression of the abnormal allele (or lack of full expression of the normal allele) can disrupt this process.

Either mechanism presupposes that we consider X-linked retinoschisis primarily as a disorder of retinal development rather than as a dystrophic process. This is certainly consistent with the clinical observations of the disorder in affected males whose onset appears to be from birth and whose progression reflects a slow and gradual deterioration of retinal function and structure.

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OPHTHALMIC MINIATURE

Cure of Strabismus.—Some men never injure themselves by being ridiculous. It is not every one, however, who can with impunity speak of his own acquirements, accomplishments or success, without the hazard, at least, of being called an egotist, a simpleton or a lunatic. A pamphlet has been received containing the names of "upwards of nine hundred persons operated on for the cure of strabismus or squinting, by T. J. Crossman, M.D., with introductory remarks, notices of the public press, and correspondence of patients." Well may the doctor exclaim, eyes, right, after having pocketed, as acknowledged on the 9th page, $45,000!

Boston Medical and Surgical Journal 29:123, 1843

Detection of Lymphocytes in the Vitreous Gel of Patients With Retinitis Pigmentosa

David A. Newsome, M.D., and Ronald G. Michels, M.D.

We used monoclonal antibodies against specific T cell, B cell, and macrophage antigens to detect immune system cells in the vitreous gel of retinitis pigmentosa patients. Vitreous samples were obtained by biopsy from three patients and by dissection from eight postmortem donor eyes. All samples contained CD4, T helper and CD8, suppressor cells, activated T cells, some B cells, and macrophages. About one third of the cells were nonreactive. Vitreous gel from normal controls contained mostly nonreactive cells with a few macrophages and rare T cells. These observations further indicated the nature of the cellular reaction in retinitis pigmentosa and characterized the biomicroscopically visible particulate bodies characteristically seen in the vitreous gel of these patients.

THE CLINICAL FEATURES of retinitis pigmentosa constitute a final expression of multiple pathogenetic mechanisms. The clinical hallmarks of retinitis pigmentosa include widespread changes in the retinal pigment epithelium, with or without intraretinal bone spicule type pigment migration; attenuation of the retinal vessels; progressive reduction of night and peripheral vision; and reduced or nonrecordable electroretinographic responses.[1] Other signs found with varying frequency include macular changes, posterior subcapsular cataract, optic nerve head drusen, and vitreous abnormalities.[1]

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Vitreous changes in eyes with retinitis pigmentosa have been well documented.[2-4] They may be the earliest biomicroscopic sign of retinitis pigmentosa and are present in all affected eyes.[1] Vitreous abnormalities include rope-like or focal condensations of the vitreous fibrils; particulate bodies including brown particles resembling tobacco dust and white or translucent bodies; and syneresis, lacuna formation, and collapse of the gel with posterior separation.

The cellular nature of some of the biomicroscopically visible particles in the vitreous gel of eyes with retinitis pigmentosa has recently been demonstrated by ultrastructure.[5,6] Because there is greater cellular reaction in the vitreous gel of young patients with an active disease process and greater cellular reaction in the more advanced eye of asymmetric cases, we studied the vitreous gel to determine if it contained immune system-related cells. Cells were collected by biopsy of the vitreous gel using vitrectomy techniques in three patients with advanced retinitis pigmentosa and from the vitreous gels of eight postmortem eyes.

Material and Methods

After obtaining informed consent as approved by the intramural review board, vitreous biopsy specimens were procured by using standard vitrectomy instrumentation and techniques from one eye of each of three volunteer patients with end-stage retinitis pigmentosa. Two patients had dominantly inherited disease and the third had isolated disease. Mononuclear cells from venous blood were separated by density gradient centrifugation using Percoll.

Particulate matter was collected from the vitrectomy specimens by centrifugation at 200 times gravity. The sediment was resuspended in 1.0 ml of sterile phosphate-buffered saline, mixed gently to homogeneity, and divided into aliquot portions for air drying on albumin-coated glass slides. Duplicate slides were

selected at random for Giemsa stain and subsequent microscopic examination and documentation by photomicrography. Other slides were used for reaction with monoclonal antibodies to peripheral mononuclear cell antigens. The positive reactions were detected by secondary antibody reaction with fluorescein isothiocyanate-conjugated species-specific anti-immunoglobulin G. Reacted samples were examined under an epifluorescence microscope equipped with a 35-mm camera attachment. Controls included goat and rabbit anti-human IgG as a first antibody and phosphate-buffered saline in place of a first antibody.

Postmortem vitreous specimens were obtained by careful stereomicroscope-aided dissection of the vitreous from eyes or culottes of eyes received in the laboratory between 11 and 28 hours after death. Only specimens free of visible gross contamination were used. The vitreous was measured by aspiration into a calibrated pipette and divided into aliquot portions. Portions of some specimens were used for biochemical studies described elsewhere. One-milliliter aliquot portions were exposed to a final concentration of 0.2% bovine testicular hyaluronidase in phosphate-buffered saline at 37 C for 30 to 40 minutes. This procedure freed the cells, which were then collected by gentle centrifugation as described, resuspended, and air dried on albumin-coated slides. The area on the slide bearing the air-dried material was marked with a waterproof circle. The entire area was systematically viewed through a light microscope so that all cells present could be counted.

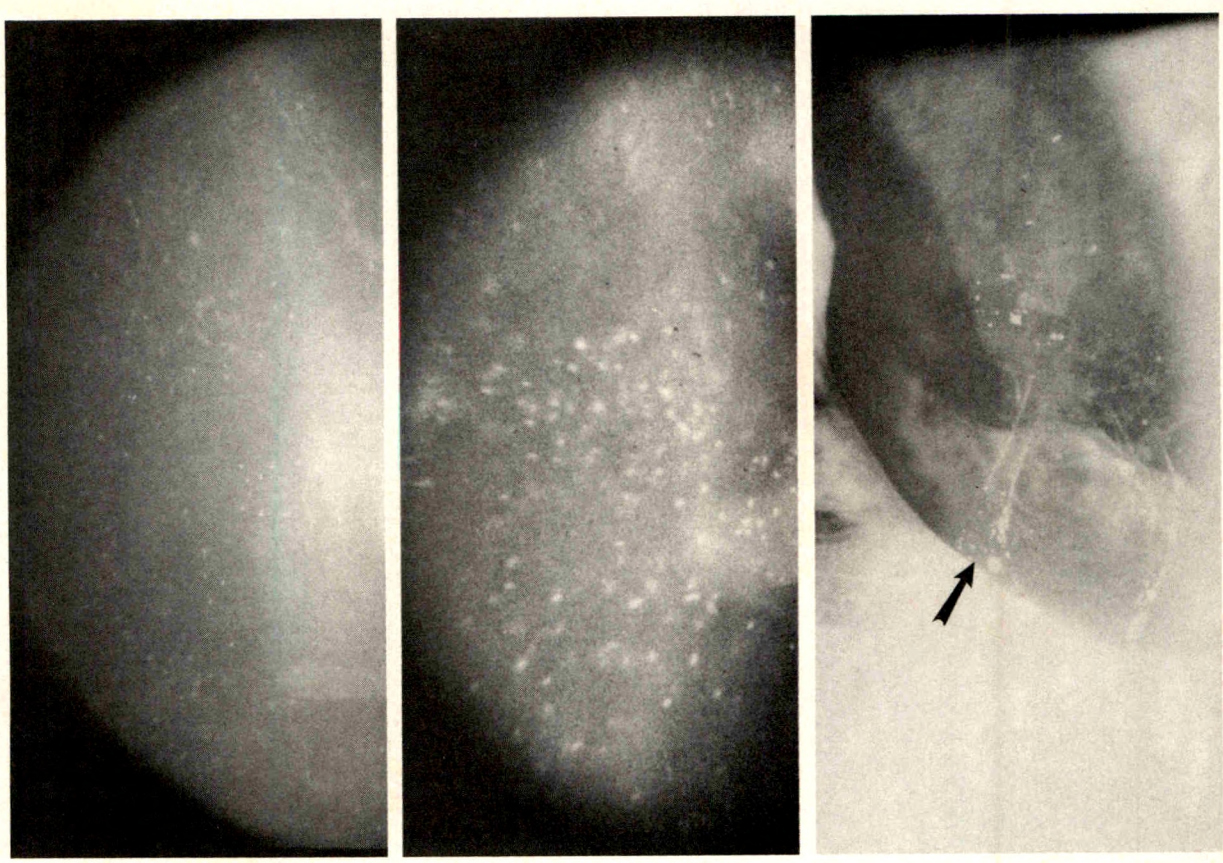


Fig. 1 (Newsome and Michels). Left, The anterior vitreous of a 31-year-old retinitis pigmentosa patient with dominantly inherited disease shows many cell-like bodies and some condensations. Middle, The anterior vitreous of a 27-year-old juvenile-onset diabetic woman, who had undergone full scatter panretinal photocoagulation three months previously, had multiple cell-like particles in the anterior vitreous. Right, The anterior vitreous face, which is partially collapsed, in the right eye of this 67-year-old woman with advanced retinitis pigmentosa shows brown particles resembling tobacco dust (arrow) or cells that appeared after intracapsular extraction.

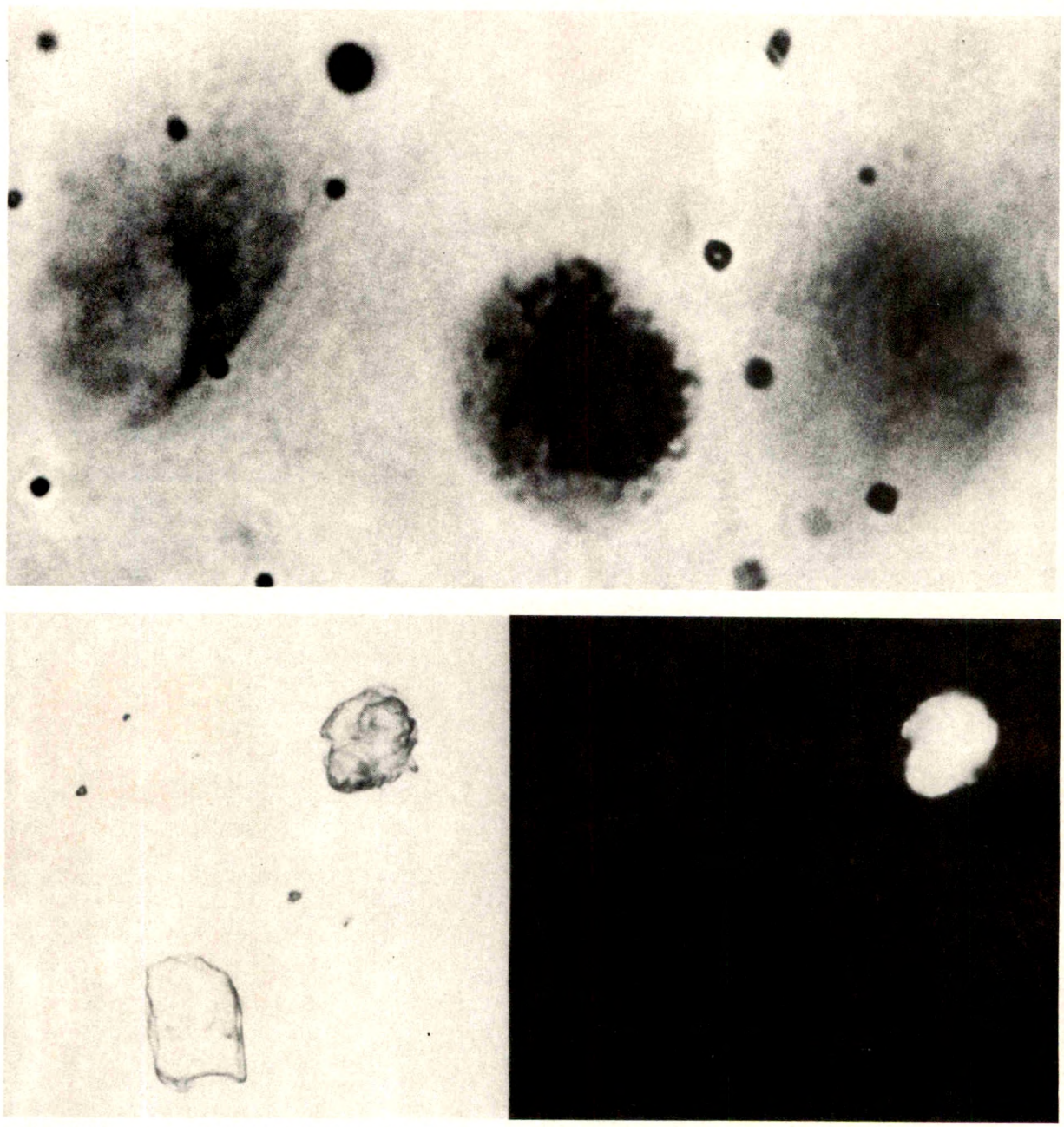


Fig. 2 (Newsome and Michels). Top, This Giemsa-stained preparation of vitreous surgically aspirated from a 68-year-old woman with retinitis pigmentosa shows three cells, the middle of which has an appearance similar to that of a peripheral blood lymphocyte (×960). The two pale-appearing cells are typical of those that did not react with anti-T cell antibodies. Bottom, The phase contrast micrograph on the left shows two cells, the upper of which fluoresced strongly after reaction with monoclonal antibody against the Leu 4 or pan T surface antigen, while the lower cell was negative (×480).

Separate 1-ml portions, after hyaluronidase digestion, were labeled with the following monoclonal antibodies: Leu 4a (pan-T lymphocyte), Leu 3a (CD4, T-helper lymphocyte), Leu 2a (CD8, T-suppressor/cytotoxic lymphocyte), HLA-DR (activated lymphocyte subset), M3 (monocyte), Leu 11c (natural killer cell), B1 (B cells). After 30 minutes of exposure to 5 μl of

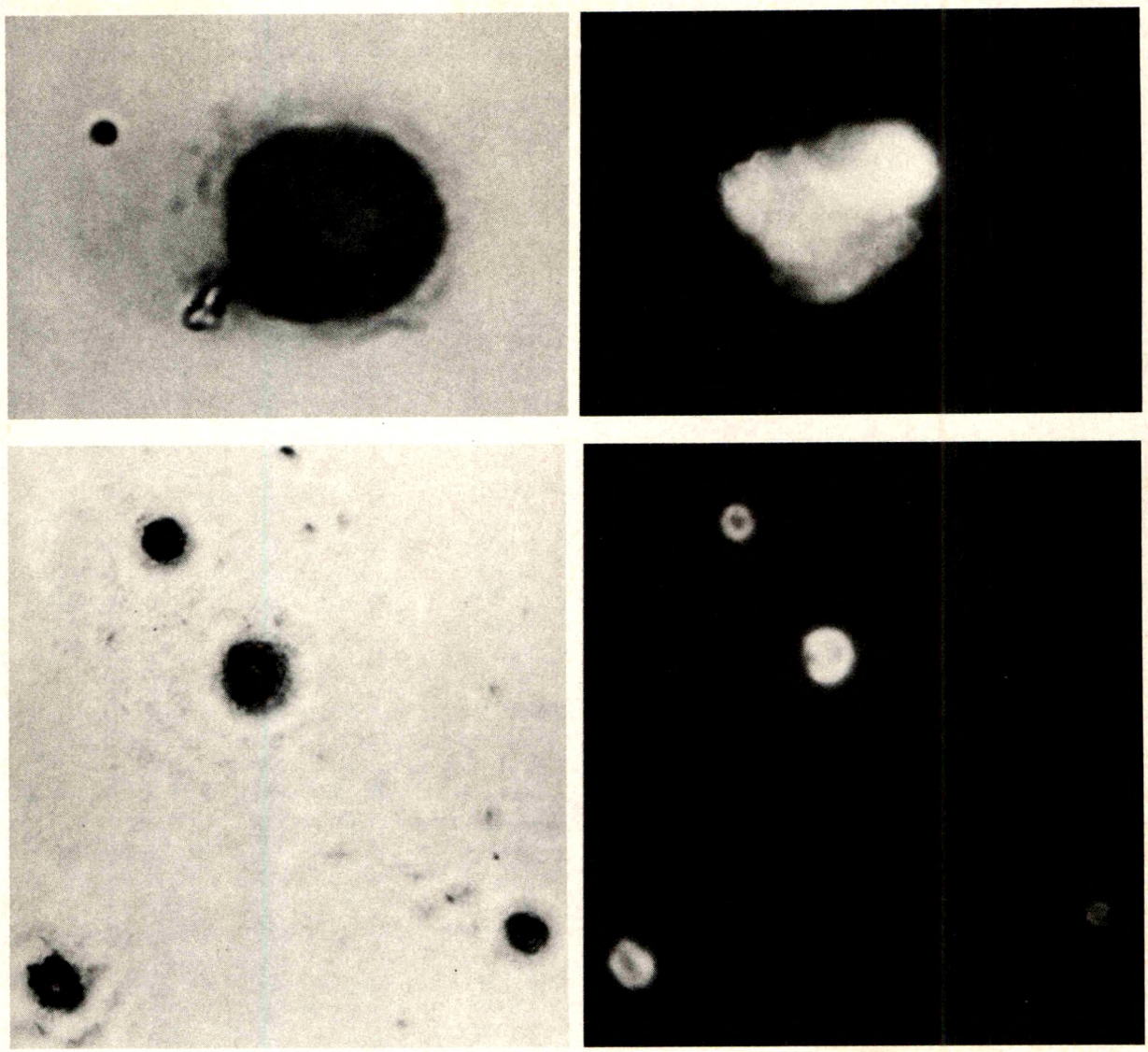


Fig. 3 (Newsome and Michels). Same patient as in Figure 2. Top, This Giemsa-stained (left, ×960) cell had an appearance resembling that of B cells and reacted positively with antibodies against B cell antigens (right, ×480). Bottom, This group of four cells freed from vitreous gel by hyaluronidase showed varying degrees of positive reactivity to antibodies recognizing natural killer antigens (×240).

the respective antibody at 4 C, the cells were washed three times in phosphate-buffered saline, resuspended in 1 ml of phosphate-buffered saline, and enumerated by flow cytometry. Forward angle and 90-degree light scatter provided identification of lymphoctyes. The percentage of positively reacted lymphoctyes was calculated by computer integration.

Control vitreous from eight grossly normal eyes of age-matched donors received at similar postmortem times was processed in the same way.

Results

All of our patients who underwent surgical removal of vitreous for study showed vitreous particles before biopsy. These particles were biomicroscopically indistinguishable from those seen in eyes of patients with other conditions (Fig. 1).

Vitrectomy specimens—A variety of lymphocyte subsets and other types of antigen-bearing mononuclear cells were present in the vitrec-

TABLE 1
PERIPHERAL BLOOD MONONUCLEAR AND VITRECTOMY-DERIVED/SPECIMEN/CELL SUBSETS

PATIENT NO.	CELLS POSITIVE WITH MONOCLONAL ANTIBODY (%) LEU 4a	LEU 3a	LEU 2a	DR	M3	LEU 11	B-1 (LEU 12)	NEGATIVE CELLS (%)
Patient 1								
Blood	72	54	17	15	2	5	0	6
Vitreous	39	27	19	8	3	8	4	39
Patient 2								
Blood	71	51	17	14	1	7	7	4
Vitreous	34	19	14	16	4	13	6	27
Patient 3								
Blood	85	57	22	8	0	0	5	4
Vitreous	31	18	16	13	3	10	7	42

tomy specimens of the three patients with end-stage retinitis pigmentosa (Table 1). The distribution of these cells had little obvious relationship to the contemporaneously determined distribution of peripheral blood subsets. Because the vitrectomy specimens were divided equally among 16 slides for air drying, it was possible to count the total number of cells per specimen. Total numbers of cells for our three specimens were 668, 1,031, and 1,428. We have no way of knowing how representative these specimens were of the entire cell population within the vitreous cavity.

Postmortem vitreous specimens—When larger quantities of excised vitreous were available, quantitative flow cytometry studies were performed. These data (Table 2) further documented the presence of various T lymphocyte subsets, B cells, and macrophage type cells in the vitreous gel of retinitis pigmentosa patients. A variable percentage of cells did not react with any of the antibodies used. By microscopic examination, these negative cells usually were larger than lymphocytes and had a different intracellular appearance (Figs. 2 and 3).

Exposure of vitreous samples to 0.2% hyaluronidase digestion did not significantly alter the detectability or type of cell surface antigen features (Table 3). No significant difference was found comparing cell subset enumerations in undigested air-dried samples with those made by flow cytometry after hyaluronidase exposure in one specimen that had enough cells to allow the comparison (Table 3).

Discussion

Investigations of immunologic mechanisms of disease have been aided by the availability of monoclonal antibodies as probes to determine the types and quantities of different subsets of lymphocytes present in the peripheral blood and in various grafts or immunologically affected organs.[7-9] The relation between types and quantities of immune cell subsets detectable in the peripheral blood compared to those in a graft or an organ such as the eye is not completely understood.[10] The nature of the retinitis pigmentosa process is uncertain, and there has been only limited evidence for an inflammatory component to this chronic, progressive retinal degenerative condition.[11,12]

We demonstrated the presence of various lymphocyte subsets along with macrophages and B cells in each of 11 vitreous specimens from retinitis pigmentosa patients. Three of the samples were obtained by vitrectomy, and therefore the detected cells were not a result of postmortem changes.

In our specimens, T cells were more numerous than other cell types. Kaplan, Aaberg, and Keller,[13] in vitreous samples from a heterogeneous group of ten patients with chronic idiopathic uveitis, found mostly B cells and macrophages with only a few T cells. They used immunoglobulin-coated beads to detect B cells, and E rosette formation to detect T cells.

TABLE 2
CELL SUBSETS DETECTED IN NORMAL POSTMORTEM AND RETINITIS POSTMORTEM VITREOUS (MEAN ± S.E.M.)

POSTMORTEM VITREOUS SPECIMEN	NO.	CELLS POSITIVE WITH MONOCLONAL ANTIBODY (%) LEU 4a	LEU 3a	LEU 2a	DR	M3	LEU 11	B1	NEGATIVE CELLS (%)
Control	8	6 ± 0.8	4 ± 0.7	1 ± 0.2	0	2 ± 0.3	0	0	93 ± 4.2
Retinitis pigmentosa	8	36 ± 7.9	25 ± 3.2	15 ± 2.6	9 ± 2.9	3 ± 0.2	9 ± 1.9	6 ± 1.2	31 ± 5.1

TABLE 3
DETECTION OF PERIPHERAL BLOOD LYMPHOCYTES AND POSTMORTEM DONOR VITREOUS CELL SURFACE ANTIGENS

	PERCENTAGE OF CELLS BY FLOW CYTOMETRY	
SPECIMEN	UNTREATED	HYALURONIDASE 0.2%
Patient 1, blood		
Leu 4a	25	24
DR	2	2
Leu 4a and DR	1	0
Negative cells	73	73
B1 (Leu 12)	3	2
M3	0	0
Leu 12 and M3	0	0
Patient 2, blood		
Leu 4a	73	79
DR	2	2
Leu 4a and DR	2	2
Negative cells	24	19
B1 (Leu 12)	5	3
M3	0	0
Leu 12 and M3	0	0
Normal vitreous		
Leu 4a	7	9
DR	0	1
B1 (Leu 12)	0	0
M3	2	2
Negative cells	91	88
Retinitis pigmentosa vitreous*		
Leu 4a	38	37
DR	7	9
B1 (Leu 12)	6	6
M3	18	19
Negative cells	31	29

*For this donor, undigested aliquot portions of vitreous were allowed to air dry on albumen-coated slides and were reacted in duplicate with the same panel of monoclonal antibodies. Cells were enumerated by epifluorescence/phase contrast microscopy, results of the two slides with the same antibody pooled, and percentages calculated: Leu 4a, 33% (34/103); DR, 6% (6/93); B1 (Leu 12), 4% (4/89); M3, 20% (20/97).

In contrast to the report of Albert, Pruett, and Craft,[6] pigment-bearing cells were present only occasionally in our cases, and no cells appeared to be uveal melanocytes by light microscopy. The vitreous samples from postmortem donor retinitis pigmentosa eyes contained occasional cells bearing macrophage antigens and rare T cells. The numbers of cells detected in normal vitreous samples processed in the same way as our postmortem retinitis pigmentosa specimens were consistently much lower than in the retinitis pigmentosa cases.

Clinical observers have noted vitreous condensations and particles in eyes with retinitis pigmentosa.[3,4] The larger particles, especially those that appear translucent in retroillumination, are now known to be cells of various types including lymphocytes. The protein content and especially the fibronectin content of the vitreous are increased in retinitis pigmentosa patients as compared with normal controls.[5] Fibronectin is known to participate in cellular attachment to collagen and in collagen cross linking. Vitreous contains epithelially derived collagen[14-16] and glycosaminoglycans.[17] The presence of fibronectin and other attachment factors interactive with vitreous collagen or other macromolecules may explain the constant association of vitreous condensations with the retinitis pigmentosa process. Serum-derived proteins and molecules such as fibronectin,[12,18] as well as putative native vitreous molecules,[19] have been shown to be mitogenic[20] or chemotactic for various cells, including immune system and pigment epithelial cells. In early and probably later stages of retinitis pigmentosa there is breakdown of the blood-ocular barrier.[21,22] This probably accounts for the presence of unusual amounts and types of proteins in the vitreous gel of retinitis pigmentosa patients.

Vitreous from eyes with proliferative vitreoretinopathy, which like the retinitis pigmentosa process is associated with breakdown of the blood-ocular barrier, has been shown to stimulate cell migration.[23,24] This suggests that the cells in the vitreous gel of retinitis pigmentosa patients could be a secondary phenomenon, like the epiretinal membrane formation that is also common.[1,25] Cell migration is a nonspecific finding, since some cells are often present in the vitreous gel of severely myopic and diabetic individuals, especially after panretinal photocoagulation.[26] However, once present in the vitreous gel, the cells may exert a variety of influences through the production of chemoattractant, degradative, or other molecules.[27-29] Thus, the immune cells that we detected in vitreous specimens from patients with retinitis pigmentosa may play a primary, active role or a secondary, passive role in the degenerative process. Further characterization of the role of intravitreal cells in the retinitis pigmentosa process requires additional study.

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A Familial Study of the Inheritance of HLA-B27-Positive Acute Anterior Uveitis

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To determine whether factors besides HLA-B27 play a pathogenic role in acute anterior uveitis, we examined 152 first-degree relatives of 42 randomly selected HLA-B27-positive acute anterior uveitis patients. Nine relatives, all from different families, had acute anterior uveitis: eight were HLA-B27 positive and one was HLA-B27 negative. The prevalence of acute anterior uveitis in HLA-B27-positive first-degree relatives of HLA-B27-positive acute anterior uveitis patients was 13% (eight of 63). This is significantly more ($P < .0001$) than the frequency of 1% in the normal HLA-B27-positive Dutch population.

Ankylosing spondylitis was found in four of 38 (11%) HLA-B27-positive family members over the age of 45 years. This is also significantly more than the prevalence of 1% in a normal HLA-B27-positive Dutch population. Of these four relatives with ankylosing spondylitis, three also had acute anterior uveitis. It was remarkable that two of these four relatives had a proband who had no ankylosing spondylitis.

A STRONG ASSOCIATION exists between acute anterior uveitis and HLA-B27. HLA-B27 has been found in approximately 50% of acute anterior uveitis patients in contrast to only in 8% of the normal population.[1] The prevalence of acute anterior uveitis in an open population was found to be 0.1% to 0.2%,[2] but in an epidemiologic survey among 10,500 Dutch inhabitants, Linssen[3] found an increased prevalence of 1% acute anterior uveitis in the HLA-B27-positive population.

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A clustering of acute anterior uveitis patients has been observed in some families,[4,5] which, in most cases, was associated with HLA-B27.[6,7] This association was not the effect of certain HLA-B27 subtypes, since acute anterior uveitis does not associate more frequently with one particular subtype.[8] It is not yet known whether the increased number of acute anterior uveitis patients in these families is simply the result of the large number of HLA-B27-positive members or whether it is the result of additional familial factors. A familial study of ankylosing spondylitis indicated that several genetic factors are probably of importance.[9] In acute anterior uveitis, genetic[10,11] and environmental[12,13] factors have been mentioned as important, but the data have not been reproduced.

In the present study we analyzed the frequencies of acute anterior uveitis and ankylosing spondylitis in first-degree relatives of randomly selected HLA-B27-positive acute anterior uveitis patients to determine what factors, if any, play a role in the pathogenesis of HLA-B27-associated acute anterior uveitis.

Patients and Methods

As described previously,[14] acute anterior uveitis patients from three university departments of ophthalmology were referred for rheumatologic examination by one of us (A.L.). All HLA-B27-positive acute anterior uveitis patients, with known addresses, were invited by letter to participate in a familial study. Those who did not respond initially received a telephone call or a second letter. A total of 85 patients were approached and 42 families agreed to participate. We received no response from 14 patients, 16 refused, one had died, and 12 patients were excluded despite their willingness to cooperate because they did not have any first-degree relatives living in The Netherlands.

There were 42 B27-positive probands with acute anterior uveitis, of whom 21 (50%) also

had ankylosing spondylitis (Table 1). First-degree relatives over 15 years of age were invited to participate in the study by the probands, to promote privacy. They were informed that participation was of scientific interest only. They were asked to answer a general questionnaire and to undergo history taking, blood sampling, and x-rays. Written consent was obtained from all relatives before participation in the study.

A pilot study of probands and relatives of the first seven families showed that results obtained via the questionnaire and a careful history taking were concordant with ophthalmologic and rheumatologic physical examination for acute anterior uveitis and ankylosing spondylitis. Thereafter, family members underwent a physical examination only when results obtained via the questionnaire and history showed positive indications of acute anterior uveitis and ankylosing spondylitis.

When possible, we used our own judgment to make diagnoses and, if symptoms were no longer present, by consulting the physician who treated the relative in the active stage of the disease. The following strict criteria were used: acute anterior uveitis was defined as a unilateral inflammation of the eye, restricted to the anterior segment, with a duration of less than 12 weeks[15]; ankylosing spondylitis was diagnosed according to the New York criteria.[16]

HLA typing was performed by a lymphocytotoxicity test in microtiter plates on nitrogen frozen and stored peripheral blood lymphocytes.[17] The percentage of HLA-B27-positive relatives was estimated after HLA typing more than half of the families, including all families in which acute anterior uveitis or ankylosing spondylitis was found.

TABLE 1
AGE AND SEX DISTRIBUTION OF
42 HLA-B27-POSITIVE PROBANDS

PROBAND	SEX M	SEX F	MEAN ± S.D. AGE (YRS)
Acute anterior uveitis only	12	9	42 ± 16
Acute anterior uveitis and ankylosing spondylitis	15	6	38 ± 13
Total	27	15	40 ± 14

The hospital ethics committee approved the use of x-rays of the sacroiliac joint in a 25-degree craniocaudal fashion in all relatives over 15 years of age. X-rays of probands and family members were mixed thoroughly and read twice independently and in a masked fashion by two of us (P.J.F.M.D. and A.L.). Discrepancies were solved by a common restudy. Occasionally, oblique planigrams of the sacroiliac joints were performed to distinguish ankylosing spondylitis from other disease processes.

Statistical analysis was performed by chi-square test using Yates' correction when necessary.

Results

Of 169 first-degree relatives living in The Netherlands who were contacted by the 42 B27-positive probands, 152 (90%) cooperated in the study. Class I HLA typing of 82 relatives from 24 families showed that 34 (41%) were HLA-B27 positive. Therefore, the estimated number of HLA-B27-positive relatives in the group of 152 relatives was 63.

Among the 152 relatives, nine (6%) (six women and three men), all from different families, had acute anterior uveitis (Table 2). One relative with acute anterior uveitis was HLA-B27 negative. The prevalence of acute anterior uveitis in B27-positive relatives was 13% (eight of 63). This is significantly increased ($P < .0001$)

TABLE 2
ACUTE ANTERIOR UVEITIS AND
ANKYLOSING SPONDYLITIS
AMONG FIRST-DEGREE RELATIVES
OF HLA-B27-POSITIVE PROBANDS*

RELATIVES	21 PROBANDS WITH AAU ONLY NO.	AAU	AS	21 PROBANDS WITH AAU AND AS NO.	AAU	AS	ALL 42 PROBANDS NO.	AAU	AS
Fathers	6	1	2	14	1	1	20	2	3
Mothers	10	1	0	15	3	1	25	4	1
Brothers	12	0	0	21	0	0	33	0	0
Sisters	18	1	0	11	1	0	29	2	0
Sons	13	1	0	9	0	0	22	1	0
Daughters	11	0	0	12	0	0	23	0	0
Total	70	4	2	82	5	2	152	9	4

*AAU, acute anterior uveitis; AS, ankylosing spondylitis.

when compared to a frequency of 1% in the normal HLA-B27-positive Dutch population.[3] Among the group of 38 relatives over 45 years of age, seven (18%) HLA-B27-positive members with acute anterior uveitis were found.

In multiple-case families, no relationship was found between the times of onset of acute anterior uveitis attacks in different individuals (Table 3). Seven of nine acute anterior uveitis patients, who developed acute anterior uveitis after their relative, lived in separate households at the time of their first attack. No relationship was found between exacerbations of acute anterior uveitis among family members.

Of 152 relatives, 111 agreed to undergo sacroiliac and lumbar x-rays. Ankylosing spondylitis was found in four HLA-B27-positive members. Since 41 relatives refused x-rays, we cannot exclude the possibility of symptomless sacroiliitis; however, none of these relatives complained of backache and we, therefore, assumed that they did not meet the full criteria for ankylosing spondylitis. The prevalence of ankylosing spondylitis in all first-degree relatives over 15 years of age was 3% (four of 152). This is significantly increased when compared to the prevalence of 0.1% in the normal Dutch population ($P < .0001$). The prevalence of ankylosing spondylitis in B27-positive relatives over 15 years of age was 6% (four of 63) and over 45 years of age was 11% (four of 38). The latter prevalence is also significantly increased ($P < .01$) when compared to the frequency of 1.3% in a normal B27-positive population over 45 years of age.[9]

TABLE 3
ONSET AND LOCATION OF ACUTE ANTERIOR UVEITIS IN PROBANDS AND AFFECTED RELATIVES IN NINE MULTIPLE-CASE FAMILIES

FAMILY NO.	PROBAND			RELATIVE			HOUSEHOLDS AT FIRST ATTACK
	BIRTH	FIRST ATTACK	LAST ATTACK	BIRTH	FIRST ATTACK	LAST ATTACK	
1	1965	1983	1984	1938	1970	—	Common
2	1955	1985	1986	1927	1952	1970	Common
3	1961	1985	—	1936	1975	—	Separate
4	1960	1983	1984	1928	1986	—	Separate
5	1946	1981	1985	1940	1985	—	Separate
6	1948	1985	1986	1915	1980	—	Separate
7	1939	1959	1987	1935	1970	1985	Separate
8	1961	1986	—	1927	1986	1986	Separate
9	1954	1983	1986	1924	1980	1986	Separate

The combination of acute anterior uveitis and ankylosing spondylitis was found in three relatives (a father from a proband with acute anterior uveitis only and a father and a mother from probands with both acute anterior uveitis and ankylosing spondylitis). Ankylosing spondylitis was found with equal frequency in families, regardless of whether the proband had ankylosing spondylitis.

Discussion

Acute anterior uveitis occurs in 1% of normal HLA-B27-positive Dutch individuals. We found a 13% prevalence of acute anterior uveitis among the HLA-B27-positive relatives of HLA-B27-positive acute anterior uveitis patients. This clearly shows an increased acute anterior uveitis susceptibility for members of HLA-B27-positive acute anterior uveitis families. This familial increase could be explained by additional genetic or environmental influences. No definite proof for either theory could be obtained in this study, although it is probable that genetic factors are of major importance since strong exclusive evidence for environmental factors was obtained.

From environmental, infectious agents in general, clustering of patients in both place and time is expected. This was not borne out in our study and, although triple- and quadruple-case families can be found occasionally, in randomly chosen families, most only have one or possibly two patients. Additionally, we found no indication that the proband infected the relative or vice versa. Therefore, since episodes of acute anterior uveitis in multicase families show no obvious relationship, the importance of environmental factors, for which seasonal variation is suggestive,[15] are surpassed by the influence of genetic factors. However, infectious agents with long incubation periods are difficult to exclude in studies of this kind and must always be considered until proven otherwise.

A hypothetical genetic factor is probably not located near the HLA-B27 locus on chromosome 6, and it was not found on chromosome 14q.[18] Despite study for the last 15 years, we can only definitively say that HLA-B27 is not sufficient for the development of acute anterior uveitis.

HLA-B27-positive and HLA-B27-negative acute anterior uveitis differ in many respects. For example, HLA-B27-positive acute anterior

uveitis is more frequently found in males, at a younger age, for a longer duration, and with a longer period of time between attacks than HLA-B27-negative acute anterior uveitis. HLA-B27-positive and HLA-B27-negative acute anterior uveitis may well be two separate diseases resulting in almost identical symptoms. Therefore, we cannot disregard the one HLA-B27-negative acute anterior uveitis patient among the members of these families. This observation could be the basis for further study into the origin of acute anterior uveitis. However, larger groups with more patients are needed, since a sole HLA-B27-negative acute anterior uveitis patient among 152 individuals does not indicate a significantly increased prevalence (normal prevalence, 1:1,000) and, since HLA-B27-positive individuals are overrepresented some fivefold in comparison with the normal population, the proportion of HLA-B27-positive and HLA-B27-negative acute anterior uveitis patients is almost equal to the normal population.

An increased prevalence of ankylosing spondylitis was found in the family members of our probands. The ankylosing spondylitis patients were distributed equally over the family groups, regardless of whether the proband had ankylosing spondylitis. This probably indicates that ankylosing spondylitis and acute anterior uveitis are more closely related than via HLA-B27 alone. Future studies are needed to elucidate the true relationship between HLA-B27 and its associated diseases.

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Immunopathologic Study of Vogt-Koyanagi-Harada Syndrome

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We studied an enucleated eye from a patient with a 30-year history of Vogt-Koyanagi-Harada syndrome using both conventional and immunohistochemical techniques. Clinically, the eye was in the end stage of Vogt-Koyanagi-Harada syndrome, and was characterized by the absence of inflammation, large areas of chorioretinal scarring, and pigmentary changes. Histopathologic examination showed marked retinal gliosis, extensive chorioretinal adhesion and scar formation, migration of pigment into the retina, and severe retinal pigment epithelial changes. However, foci of mild to moderate nongranulomatous inflammation of the uvea were observed. These foci contained infiltrating cells that were mainly T lymphocytes with B lymphocyte aggregates at the center. Scattered macrophages were also noted in the uvea and retina. These findings suggest that both the cell-mediated and humoral immune arms may play roles in the pathogenesis of Vogt-Koyanagi-Harada syndrome.

Vogt-Koyanagi-Harada syndrome is a bilateral panuveitis with exudative retinal detachment, associated with poliosis, dysacousia, alopecia, vitiligo, cerebrospinal fluid pleocytosis, and meningeal signs.[1-4] It occurs more frequently in Orientals than in whites and comprises about 4% of patients with uveitis seen in a clinic located in Chicago.[5] Vogt-Koyanagi-Harada syndrome has been divided into the meningeal, ophthalmic, and convalescent stages according to its clinical course and manifestations.[6] Only a few histopathologic studies of eyes with Vogt-Koyanagi-Harada syndrome have been reported. Data on the immunopathologic characteristics of Vogt-Koyanagi-Harada syndrome are even more limited. We describe herein the use of monoclonal antibodies to detect immunocompetent cells and to examine the surface markers of ocular resident cells of an enucleated eye at the convalescent stage of Vogt-Koyanagi-Harada syndrome.

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Case Report

A 72-year-old black woman had a 30-year history of bilateral intermittent panuveitis with exudative retinal detachment and papilledema, the right eye worse than the left eye. Her ocular signs and symptoms became progressively worse after each recurrence. A diagnosis of Vogt-Koyanagi-Harada syndrome was made. She did not respond to systemic prednisone, chlorambucil, or fever therapy. The patient underwent a peripheral iridectomy for angle-closure glaucoma caused by lens subluxation in her right eye in 1976, and cataract extraction in her left eye in 1981. However, from 1978 to 1982 her visual acuity gradually deteriorated to no light perception in her right eye and 20/200 in her left eye because of the inability to control her Vogt-Koyanagi-Harada syndrome. She then experienced a decrease of hearing and loss of skin pigmentation. In 1983 the ocular inflammation subsided and she has not taken any anti-inflammatory medications since 1984. In 1984 the ocular examination showed reattached atrophic retina, with multiple chorioretinal scars distributed in a geographic pattern. Marked pigmentary alterations and abnormal arrangement with hyperpigmentation and depigmentation were seen in the fundus (Fig. 1). In 1985 her right eye developed neovascular glaucoma, exotropia, and became painful. It was enucleated a few months later.

Material and Methods

The globe was opened horizontally immediately after enucleation. It was then cut through the anterior peripheral retina and divided into

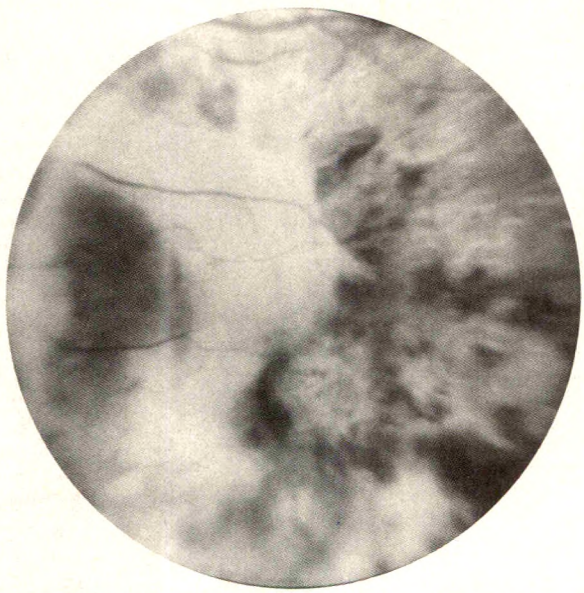


Fig. 1 (Chan and associates). Clinical examination showed marked pigmentary changes at the level of the atrophic retina and multiple chorioretinal scar formations.

four portions. One of the anterior portions included the cornea, angle, iris, and ciliary body, and one of the posterior portions included the retina, choroid, and sclera, which were removed for immunohistochemical study. They were snap frozen and embedded in OCT compound. Frozen serial sections 6 μm thick were prepared by using the avidin-biotin-peroxidase technique.[7] The primary antibodies were monoclonal antibodies prepared against human pan T lymphocytes (Leu 4), T helper/inducer lymphocytes (Leu 3a), T helper/inducer lymphocytes with inducer function (Leu 8), T suppressor/cytotoxic cells (Leu 2a), T suppressor/cytotoxic cells with suppressive function (Leu 15), B lymphocytes (Leu 14), bone marrow-derived monocytes (macrophages and epithelioid cells, OKM1, and Leu M5), natural killer cells (Leu 7), anti-major histocompatibility complex class II antigens (HLA-DR and Leu 10 for HLA-DQ), interleukin 2 receptors (II-2Rs) (anti-TAC), and anti-interferon-gamma (IFN-γ). Mouse ascitic fluid containing 1 to 2 mg/l of protein served as a control. The secondary antibody was biotin-conjugated horse anti-mouse IgG. The avidin-biotin-peroxidase solution was applied, and the substrate was diaminobenzidine-nickel sulfate-hydrogen peroxide.

The remaining portions of the specimen were subdivided for light and electron microscopy. They were fixed in 2.5% glutaraldehyde. For light microscopy, the specimens were embedded in glycol methacrylate, and 3-μm sections were stained with hematoxylin and eosin or periodic acid-Schiff. For transmission electron microscopy the specimens were embedded in an epoxy resin. Ultrathin sections were stained with uranyl acetate-lead citrate.

The patient's serum was diluted in Tris buffer (pH 7.6) 1:40 as the primary antibody to stain on the normal human frozen retinal tissue to detect the presence of autoimmune antiretinal antibodies by indirect immunoperoxidase technique as described previously.[8]

Results

Macroscopic examination of the right globe demonstrated an opaque cornea, shallow anterior chamber, and aphakia. A white calcified piece measuring about 5 mm in diameter was attached to the peripheral superior retina. This firm material dissolved instantly in decalcifying solution containing formic acid. The extremely thin retina was attached. The fundus showed an irregularly mottled appearance with varying pigmentation.

Microscopic examination disclosed a few foci of amyloid deposits in the mildly edematous cornea. The angle was covered by a thin hyalinized tissue. The iris was mildly infiltrated with lymphocytes. A scar-like hyalinized tissue was seen at the posterior central iris. The ciliary body was atrophic and hyalinized. The thin and gliosed retina was adherent to a hyalinized tissue consisting of layers and islands of pigmented and nonpigmented epithelial cells. In some areas a preretinal membrane was observed. Bruch's membrane was not identified. The site from which calcified materials had dissolved showed a thickened membranous tissue. The optic nerve was atrophic. The choroid had lost its capillary structure and choroidal melanocytes were rarely present. Focal areas of mild to moderate lymphocytic infiltration were observed in the choroid (Fig. 2). A small number of plasma cells were also seen.

Electron microscopic examination of a small portion of the retina demonstrated thin, membranous glial cells. Beneath the gliotic retina the pigmented cells and the surrounding loose connective tissue contained abundant calcium particles. No organisms were observed.



Fig. 2 (Chan and associates). Histopathologic examination showed extensive retinal gliosis, and preretinal membrane. Left, Multilayers of retinal pigment epithelial cells (rpe). Right, A cluster of lymphocytic infiltration in the choroid (left and right: hematoxylin and eosin, ×500).

Immunohistopathologic studies showed mild to moderate inflammatory cells in the choroid and a few in the atrophic retina with T lymphocytes and foci of B cells (Fig. 3). Among the T lymphocytes, the ratio of T helper/inducer to T suppressor/cytotoxic cells was 1.5:1. Scattered macrophages were observed in the uvea and retina. The retina stained strongly with glial fibrillary acidic protein, an element of glial filament, and an indication of retinal gliosis. The expression of major histocompatibility class II antigens (HLA-DR and -DQ) was observed occasionally on the corneal keratocytes, uveal and retinal vascular endothelial cells, and retinal pigment epithelial cells. No retinal glial cells stained for HLA-DR or HLA-DQ.

The patient's serum demonstrated a weak reaction to outer segments of the photoreceptors, but not to Müller cells of the normal human retina, as measured by an indirect immunoperoxidase technique.

Discussion

The patient described herein is typical of patients with long-standing Vogt-Koyanagi-Harada syndrome. She suffered from bilateral progressive panuveitis with recurrent exudative retinal detachments for 30 years. The patient also developed dysacousia and vitiligo. The time sequence was unusual because this patient developed these symptoms late in her disease, which suggests that the disease had been constantly active for more than 20 years.

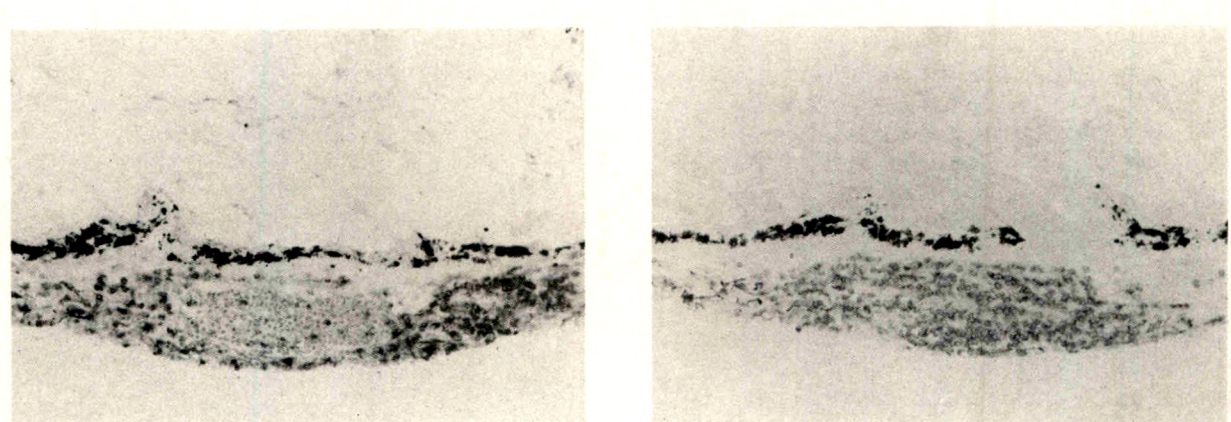


Fig. 3 (Chan and associates). Immunohistochemical examination showed a foci of B lymphocytes surrounded by T helper lymphocytes in the choroid. Left, Leu 3a; right, Leu 14 (left and right: avidin-biotin-peroxidase, ×500).

The histopathologic appearance of her right eye was consistent with the convalescent or end stage of Vogt-Koyanagi-Harada syndrome, characterized by a markedly gliosed retina adhering to the proliferative retinal pigment epithelia and the scarred choroid. In general, the histopathologic findings of Vogt-Koyanagi-Harada syndrome in the ophthalmic stage resemble those seen in sympathetic ophthalmia with uveal granulomatous inflammation and formation of Dalen-Fuchs' nodules.[4,9,10] Unlike sympathetic ophthalmia, the histopathologic characteristics of Vogt-Koyanagi-Harada syndrome seen in the convalescent stage also include obliteration of the choriocapillaries, focal active nongranulomatous or granulomatous chorioretinitis, chorioretinal scarring, marked retinal gliosis, destruction of photoreceptor layers, and extensive retinal pigment epithelial involvement.[10-12] Retinal pigment epithelial cells may undergo hypertrophic and hyperplastic changes, with proliferation and migration into the gliotic retina. They may also show hypotrophic and atrophic alterations. Inflammatory cells in the iris and ciliary body have been described in long-standing cases of Vogt-Koyanagi-Harada syndrome and are believed to prolong the ocular inflammation.[12] However, our patient had minimal lymphocytic infiltration in the iris and significant collections of lymphocytes in the choroid as well as a scattered monocytic infiltration in the retina, despite the clinically quiescent eye at the time of enucleation.

Immunohistochemical study showed that the predominant, infiltrating cells were T lymphocytes, which were also the main component found in the eyes with sympathetic ophthalmia.[7,13-15] Reports on the surface markers of peripheral blood and cerebrospinal fluid lymphocytes of patients with Vogt-Koyanagi-Harada syndrome demonstrate an increase of T lymphocytes, and especially T helper/inducer cells, in cerebrospinal fluid compared with blood.[16-19] Aniga and associates[19] found T lymphocytic infiltration in the corneoscleral limbus and skin with vitiligo in four patients with Vogt-Koyanagi-Harada syndrome. They interpreted the T lymphocyte as being the most important cellular subtype in the delayed-type hypersensitivity immune reaction, with this cell migrating to the inflammatory site, such as cerebrospinal fluid, skin, and corneoscleral limbus. Our results on the predominant T cell infiltration in the eye also suggest that Vogt-Koyanagi-Harada syndrome may be involved in a cell-mediated immune response. However, the accumulation of B lymphocytes, scattered distribution of macrophages, and presence of plasma cells were noted in the present case but have not been reported in sympathetic ophthalmia.[7,13-15] Weak antiretinal antibodies were also detected in her serum. These findings suggest that humoral immunity may play certain roles in Vogt-Koyanagi-Harada syndrome that are not as evident in sympathetic ophthalmia.[20]

There was a lack of expression of major histocompatibility complex class II antigens (HLA-DR and HLA-DQ) on the retinal pigment epithelium, glial cells, and fibroblasts in this eye. Expression of these antigens on the resident cells in the inflamed target organ has been hypothesized to play an important role in the initiation and perpetuation of various organ-specific autoimmune processes.[21-23] However, at the late or end stage of the inflammation, these antigens may disappear on resident cells, as seen in the late stage of an experimental autoimmune uveoretinitis model.[23] Thus, our result seems consistent with end-stage Vogt-Koyanagi-Harada syndrome.

Loss of choroidal melanocytes was believed to be caused by ocular inflammatory cells, possibly the lymphocytes seen in Vogt-Koyanagi-Harada syndrome.[4,12] In the present case, most of the choroidal melanocytes had disappeared, which may have been the result of the damage caused by the ocular inflammation. Although the precise immunopathogenesis of Vogt-Koyanagi-Harada syndrome has yet to be defined, the present findings emphasize the delicate balance between the potential importance of the T cell-mediated immune processes and the humoral immune response in an eye with Vogt-Koyanagi-Harada syndrome. Additional immunologic and immunohistopathologic evaluations of the ocular, dermal, and auditory tissues of patients with Vogt-Koyanagi-Harada syndrome in different clinical stages are needed to better understand the mechanisms of this disorder.

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Magnetic Resonance Imaging of Nonmetallic Orbital Foreign Bodies

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We studied a cadaver head model in which we inserted three orbital foreign bodies. We chose these foreign bodies because of their similarity to substances found in orbital trauma. Teflon and Lucite were used to represent synthetic materials, and dry pine was chosen as a type of organic material. Lucite is similar in radiographic density to plastics used in interior trim for automobiles and spectacle frames. While both orbital ultrasound and plain skull films failed to detect the foreign bodies consistently, both computed tomography and magnetic resonance imaging detected and localized the foreign bodies relatively well. Computed tomography was better in delineating shape and characterizing composition.

BEFORE COMPUTED TOMOGRAPHIC scanning was available, the localization of metallic foreign bodies in the eye was usually accomplished successfully by using a combination of Sweet's modification of orbital X-ray technique and ultrasound.[1-6] Nonmetallic intraocular foreign bodies, on the other hand, were difficult to find.[2,7] Computed tomography, however, has aided in detection.[5-7]

Although metallic orbital foreign bodies also were relatively easy to detect by X-ray before computed tomography, they were not easy to detect with ultrasound even when the gain was reduced to try to separate the fat spikes from those of the foreign body and using a 5-MHz instead of a 10-MHz head for better penetration into the orbital apex. Immersion ultrasound has helped but still has left a difficult problem in detecting metallic orbital foreign bodies.[1,2,4,5,8-11]

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Detection of nonmetallic orbital foreign bodies is just as difficult as when they are in the eye. They essentially defy detection with plain X-rays or ultrasound.[10,12,13]

Computed tomography has been reported to be the best method at present for metallic orbital foreign body detection.[5,8,11,12,14,15] However, magnetic resonance imaging has only recently been studied.[16]

Reports describing computed tomography of nonmetallic orbital foreign bodies are not common and some are limited in scope.[12-15,17] Magnetic resonance imaging studies have not yet been reported. Since both organic and inorganic nonmetallic orbital foreign bodies can cause inflammation and infection, we decided to study a cadaver model. We first looked at the sensitivity of detection, delineation of shape and localization, and secondly at the specificity of material identification. We used A- and B-mode ultrasound, plain X-rays of the skull and orbits, computed tomography, and magnetic resonance imaging.

Material and Methods

We attempted to simulate the living orbit by using a fresh, cooled adult cadaver head. The head was not embalmed in an attempt to eliminate air bubbles in the vascular system. Because the eyes were somewhat collapsed they were inflated with both saline and air. We did not think this a disadvantage since we were not studying intraocular foreign bodies. We wanted the eye detectable as a discrete entity of normal size and shape. Since skull X-rays may detect spectacle glass because of its relatively high density,[14] we chose three materials of less density to cover a range of nonmetallic foreign bodies that might gain access to the orbit in instances of facial trauma. Three substances, Teflon, Lucite, and pine, were chosen from a large number of synthetic and organic possibilities and were scanned by a similar technique

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as described by Kadir, Aronow, and Davis.[14] Teflon had a Hounsfield unit rating of +1,099; Lucite, +164; and dry pine, −660. Three locations were chosen as representative of possible foreign-body sites of localization in the orbit. The Teflon was placed under the right lateral rectus muscle insertion, Lucite was placed medial to the right medial rectus muscle, and the pine was placed in the left muscle cone.

Targets of 7 mm in size were used as a convenient size to handle and to detect.[9] A sphere was chosen because of its uniformity of shape from all viewing angles, thereby simplifying detection comparison on imaging studies. The three spheres were scanned in a water bath before being placed in the head. Ultrasound measurements were taken at that time. Images of the head and orbits were also obtained with each technique, ultrasound, skull films, computed tomography, and magnetic resonance imaging, before the foreign bodies were inserted. After these studies were obtained and the cadaver head was deemed suitable for the study, that is, no evidence of a foreign body, tumor, or other orbital problem that might be confusing, the foreign bodies were inserted.

The first orbital study was done with ultrasound, with an 8-MHz head. Tumor sensitivity (74 dB) and measuring sensitivity were both used. B-ultrasound was done with a Sonometrics unit with a 5-MHz head.

Computed tomography images in axial and coronal planes were generated. Slice thickness was 1.5 mm and slices were contiguous. The window level was between 30 and 40 and window width usually was 200 to 300. An occasional width of 1,000 was used. The matrix size was 320 × 320. Magnetic resonance imaging was done with two different midfield strength magnets, the 0.35-tesla Diasonics and the 0.5-tesla Picker. Slice thickness was 5 mm with a 256 × 256 matrix. T_1- and T_2-weighted images using a spin-echo technique were obtained in the axial plane. T_1-weighted images had a repetition time of 500 msec and an echo time of 40 msec. The T_2-weighted images had a repetition time of 2,000 or 2,200 msec and an echo time of 80 msec.

Results

All three substances had maximum A-ultrasound spikes in a water bath when the tumor sensitivity (tissue sensitivity − system sensitivity) setting was used. When quantitative echography with measuring sensitivity was used equal amplitude spikes were obtained when Teflon was tumor sensitivity −45, Lucite was tumor sensitivity −45, and pine was tumor sensitivity −38. Two living normal eyes had been used for controls with the scleral spike adjusted to tumor sensitivity −51. However, with the spheres in the orbits, it was difficult to detect any of the foreign bodies with either A- or B-scan modes. Knowing exactly where the objects were placed, it was occasionally possible to image them with either technique.

Despite considerable effort the foreign bodies were never seen on the plain skull films. All three substances were detected and localized in relation to other structures by computed tomography imaging. Shape delineation was possible unless only the edge of the sphere was imaged. Hounsfield units assisted in characterizing approximate densities of the substances. The only detection problem was that the lacrimal gland density was close to the density of Lucite (Figs. 1 and 2).

Detection of the foreign bodies was as successful with T_1-weighted images with magnetic resonance imaging as with computed tomography but localization was probably not as good. Both detection and localization were more difficult with T_2-weighted images. Delineation of

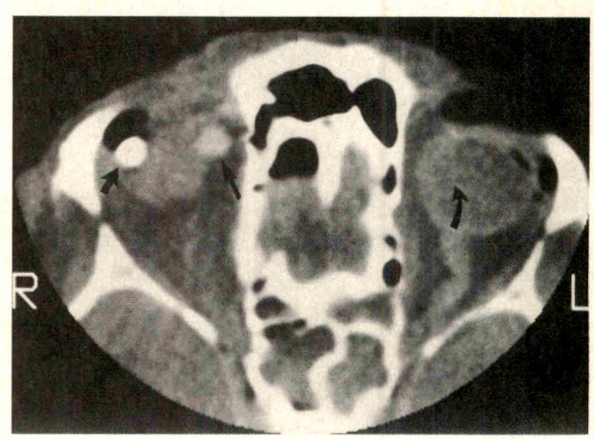


Fig. 1 (Wilson and associates). An axial computed tomograph of the midorbit shows Teflon (thick arrow) +1,099.2 Hounsfield units (white), Lucite (thin arrow) +164.4 Hounsfield units (light gray). Both are in the right orbit and both are whiter than fat. Pine (curved arrow), −660.0, is in the left orbit and is darker than fat and difficult to see in this photograph. Window level is +113 and width 1,000.

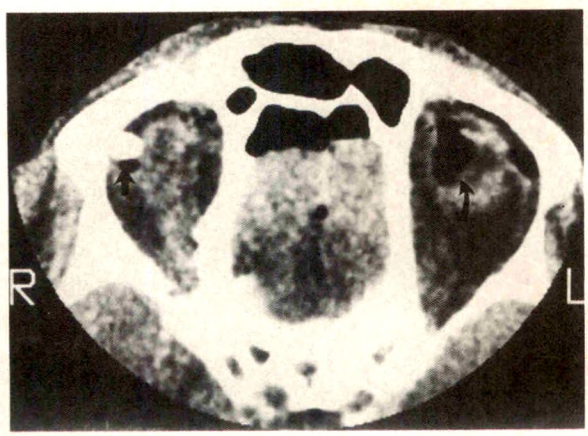


Fig. 2 (Wilson and associates). A computed tomograph of the high orbit in the axial plane, same foreign bodies. Probably Lucite is not seen. Teflon (thick arrow); pine (curved arrow). Window level is +47, width 250.

shape was not optimal with either magnetic resonance imaging sequence (Figs. 3 through 8). Composition characterization was not possible with magnetic resonance imaging. All three substances were either proton free or made up of protons that could not be moved by the radio frequency signal since their images were black.

Discussion

Detection of the foreign bodies used in this study was difficult with ultrasound as mentioned, whether with A- or B-scanning. Occasionally it was possible to find the foreign bodies using A-mode ultrasound at measuring sensitivity when one knew exactly the foreign body location. However, A-mode scanning is probably impractical since it takes so long to scan the whole orbit and the difference between the high spikes of fat and foreign body is relatively small. The difficulty with poor penetration of the orbit apex reduces the value of ultrasound even further. Localization relative to other structures, shape recognition, and composition characterization were not possible because of the detection problem mentioned above.

All of the substances had high spikes with B-mode ultrasound and it was very difficult again to separate the foreign bodies from the orbital structures on the basis of spike detail.[10]

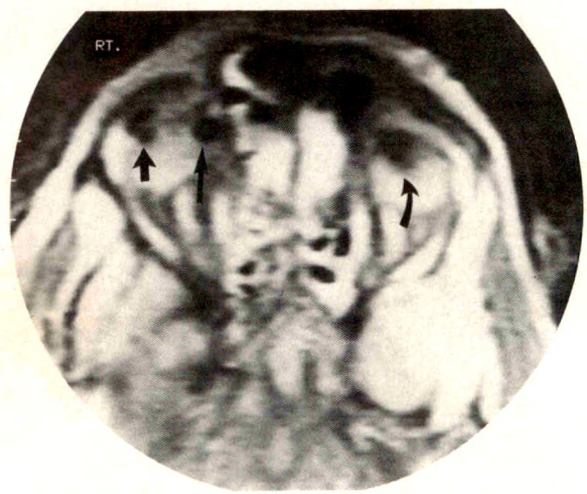


Fig. 3 (Wilson and associates). An axial Picker magnetic resonance image in the midorbit T_1-weighted. Again, the pine (curved arrow) is the most difficult to see. Teflon (thick arrow); Lucite (thin arrow). Repetition time 500 msec and echo time 40 msec.

While B-mode ultrasound was less time consuming it was no better in any other parameter than A-mode ultrasound. One added problem with B-mode ultrasound is the difficulty in imaging the anterior corners of the orbit.

Plain skull-orbital films failed to show any of the foreign bodies. We used several distances, grids, film types, and KV voltage settings but to no avail.

Computed tomography was successful in de-

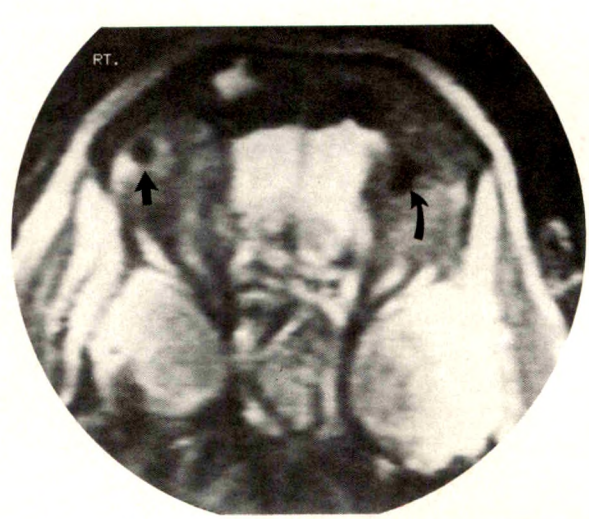


Fig. 4 (Wilson and associates). Magnetic resonance imaging as in Figure 3 but of the high orbit. Teflon (thick arrow) and pine (curved arrow) are seen.

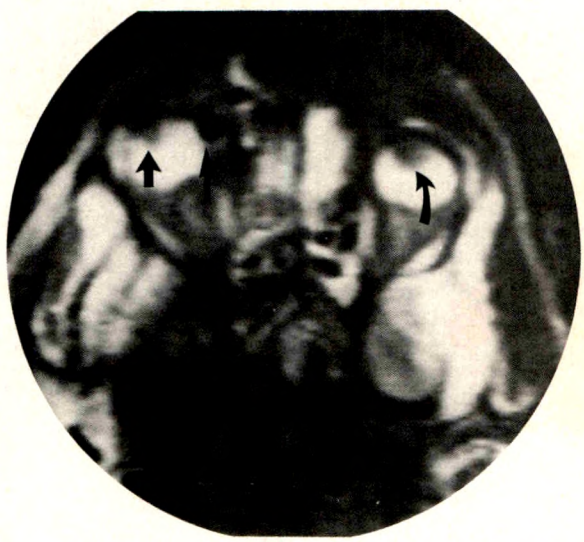


Fig. 5 (Wilson and associates). An axial Picker magnetic resonance image in the midorbit T_2-weighted. Repetition time 2,200 msec and echo time 80 msec. Teflon (thick arrow) is difficult to see and pine (curved arrow) is imaged over the white of the eye. Lucite (thin arrow).

tecting and localizing all three foreign bodies. The radiographic density of Lucite was close to that of the lacrimal gland and might pose some difficulty in separating the two. Since computed tomography gave such good edge and,

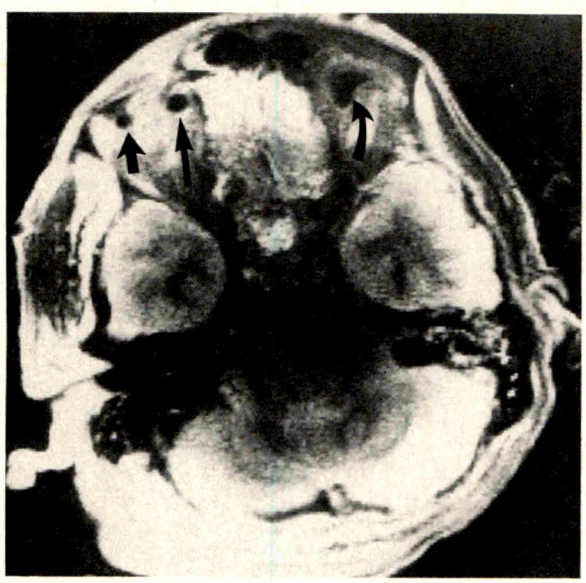


Fig. 7 (Wilson and associates). Diasonics magnetic resonance imaging. T_1-weighted (repetition time 500 and echo time 40), high orbit. All three foreign bodies can be visualized: Teflon (thick arrow), Lucite (thin arrow), and pine (curved arrow).

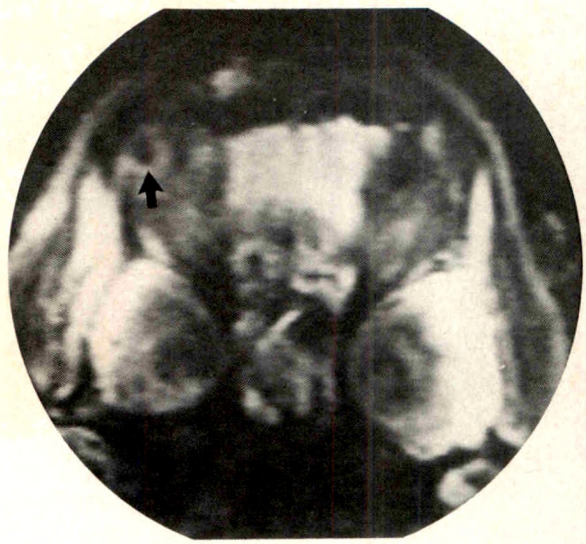


Fig. 6 (Wilson and associates). Magnetic resonance imaging as in Figure 5 but in the high orbit. Teflon (thick arrow). Lucite and pine are difficult to see.

therefore, shape delineation the exact localization in reference to the eye, optic nerve, and muscles was relatively easy. The assistance computed tomography gives in attempting to remove a foreign body is obvious. The same Hounsfield numbers we obtained for Lucite

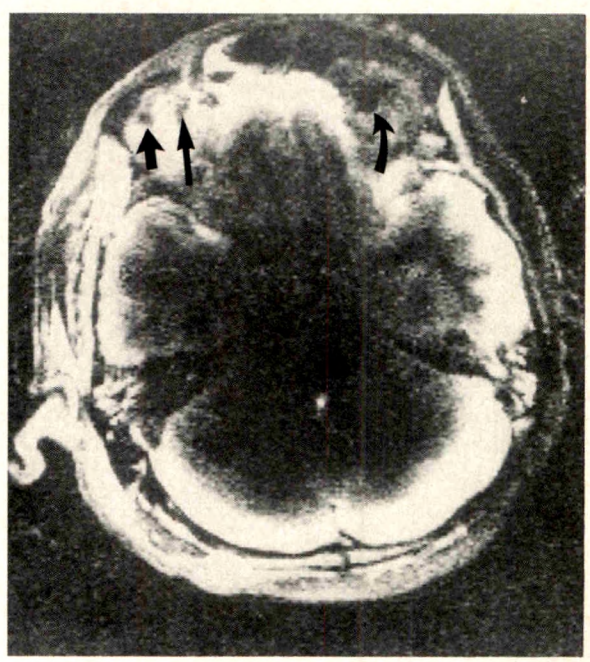


Fig. 8 (Wilson and associates). Diasonics magnetic resonance imaging. T_2-weighted (repetition time 2,000 and echo time 80). Teflon (thick arrow), Lucite (thin arrow), pine (curved arrow). Again, Lucite is the most difficult to see.

and Teflon on prescanning were found when they were in the cadaver orbit and therefore made positive identification possible. The pine had a very low density and appeared black, probably because it was dry and had a high air content. The optimum window width of computed tomography for the two plastic-like foreign bodies was between 200 and 400 and for window level, about 30 to 40. These parameters helped to separate normal structures from the foreign bodies. Although wider window widths (particularly in the negative direction) are not shown in our illustrations, they did help in differentiating pine from air.

The T_1-weighted magnetic resonance scan detected all of the foreign bodies but, since they were all hypointense (black), the foreign body had to be differentiated from other tissues with low signal intensity. Magnetic resonance imaging is often able to identify tissue on the basis of contrast sensitivity even though it may not have as good resolution sensitivity as computed tomography. In the case of the foreign bodies in this study, which were all imaged as hypointense, the effectiveness of this magnetic resonance imaging feature was reduced. In the case of trauma then, air and bone fragments would have the same signal intensity as the foreign bodies we used. The combination with computed tomography would then be helpful.

Even though the magnetic resonance imaging brightness (hyperintensity) of orbital fat was a good foil for the black (hypointense) foreign bodies of this study, edge/shape delineation was still difficult. We used dry pine in our study. If pine stayed in the orbit for days it might become hydrated with fluid and might have a different appearance. The conspicuity of the T_2-weighted images was less than that of the T_1-weighted images for all the parameters studied, probably because of the loss of signal intensity in the orbital fat.

Another drawback of magnetic resonance imaging is the danger to intraocular structures if the foreign body contains ferromagnetic substances.[18,19] In the case reported by Kelly and associates,[19] a 3-mm metallic intraocular foreign body was seen on computed tomography but not appreciated as metal and the subsequent magnetic resonance study produced vitreous hemorrhage and loss of vision. The patient died from metastatic cancer and his potential for recovery of vision is therefore unknown.

If the resolution sensitivity of the magnetic resonance imaging had been better, the ability of the computed tomography to characterize the composition of the three foreign bodies might have been offset to some degree. The newer, stronger magnets may increase the assistance magnetic resonance imaging now renders and therefore assist in those studies. For example, it may be possible to follow the progression of orbital blood after trauma using both T_1- and T_2-weighted images.

Hemorrhage has a varied appearance on T_1-weighted and T_2-weighted sequences, depending on the age of the blood and the field strength of the magnet.[20] Generally, acute hemorrhage (less than seven days) on midfield (0.35 to 0.5 tesla) magnetic resonance units is isointense to white matter on T_1-weighted and T_2-weighted pulse sequences. As the deoxyhemoglobin in the hematoma converts to methemoglobin this shortens the T_1-value and lengthens the T_2-value secondary to change in magnetic susceptibility. This causes the hematoma to become bright on T_1 and T_2 (peripheral to central). Finally, as methemoglobin converts to hemosiderin the T_1-value lengthens and the T_2-value shortens, giving hypointensity on both the T_1-weighted and T_2-weighted sequences.

The detection of nonmetallic orbital foreign bodies by imaging techniques needs further study. Other substances, other positions in the orbit, and different sizes all need to be explored.

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OPHTHALMIC MINIATURE

The commas are the most useful and usable of all the stops. It is highly important to put them in place as you go along. If you try to come back after doing a paragraph and stick them in the various spots that tempt you you will discover that they tend to swarm like minnows into all sorts of crevices whose existence you hadn't realized and before you know it the whole long sentence becomes immobilized and lashed up squirming in commas. Better to use them sparingly, and with affection, precisely when the need for each one arises, nicely, by itself.

Lewis Thomas, "Notes on Punctuation," in *The Medusa and the Snail. More Notes of a Biology Watcher*
New York, The Viking Press

Transient Proliferative Diabetic Retinopathy During Intensified Insulin Treatment

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Two women aged 22 and 19 years who had had diabetes for 11 and four years, respectively, developed proliferative retinopathy after five to seven months of significantly improved metabolic control. They were participants in two separate prospective studies including 97 insulin-dependent patients. At inclusion, one patient showed minimal background retinopathy and the other showed no retinopathy. Their level of glycosylated hemoglobin was initially high (14.3% and 17.5%) but within five to six months had fallen by 5.7% and 7.5%. The improved metabolic control was obtained by home blood glucose monitoring and insulin pump in the older patient and by home blood glucose monitoring only in the other. By maintaining near normoglycemia, regression of the proliferative retinopathy was achieved. Photocoagulation was not performed. After five and two years of follow-up, respectively, only mild background retinopathy has been noted in both patients. We concluded that a significant lowering of blood glucose may provoke proliferative retinopathy and that sustained good metabolic control may reverse this retinopathy without photocoagulation.

WORSENING OF background retinopathy on rapid intensified insulin treatment is well documented.[1-5] Prospective and randomized studies indicate that the worsening may be transient in diabetic patients who maintain good metabolic control.[6-8] Proliferative retinopathy, however, develops and progresses despite long-term near normoglycemia obtained by continuous subcutaneous insulin infusion.[1-3,9] Photocoagulation is currently the treatment of choice in both preproliferative and proliferative diabetic retinopathy.[10,11]

However, cases of reversal of already established preproliferative[12] and florid proliferative[13,14] retinopathy on continuous subcutaneous insulin infusion treatment have been reported. Herein we describe the development and regression of florid proliferative retinopathy in two young diabetic women, both of whom were participants in two separate randomized trials concerning effects of intensified insulin treatment on retinopathy.[5] Initially, the improvement in metabolic control seemed to provoke the proliferative retinopathy. However, sustained metabolic control reversed the proliferative process. Photocoagulation was not performed. We question whether photocoagulation is the obligatory form of treatment in every case of proliferative diabetic retinopathy.

Patients and Methods

Two diabetic women participated in two separate prospective studies, the Oslo study[5,8] (45 diabetics, 21 women and 24 men) and the World Health Organization multicenter continuous subcutaneous insulin infusion pump acceptability and feasibility study (52 diabetics, 29 women and 23 men) (unpublished data). All patients in both studies were between 16 and 43 years of age, did not have systemic hypertension (diastolic blood pressure ≤100 mm Hg) or nephropathy (Albustix negative), were not pregnant, and had no ocular diseases other than background diabetic retinopathy (Table).

All but four patients were receiving two insulin injections per day at the start of the studies. One patient used three insulin injections per day, and three were on a multiple insulin injec-

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TABLE
BACKGROUND CHARACTERISTICS AND METABOLIC CONTROL DURING FIVE TO SEVEN MONTHS OF INCREASED BLOOD GLUCOSE CONTROL
(N = 97)

PATIENT	AGE (YRS)	DURATION OF DIABETES (YRS)	BLOOD PRESSURE (MM HG)	URINARY ALBUMIN* (MG/24 HR)	% GLYCOSYLATED HEMOGLOBIN: INITIAL LEVEL	% GLYCOSYLATED HEMOGLOBIN: CHANGE AFTER 5 TO 7 MONTHS
Patient 1	22	11	110/80	525	14.3	−5.7
Oslo study						
Mean	26	13	124/80	20	11.1	−1.9
Range	18–42	6–23	110–160/60–100	2–525	7.5–18.9	−0.6 to −7.5
Patient 2	19	4	125/80	135	17.5	−7.5
World Health Organization study						
Mean	25	10	120/80	28	10.6	−0.4
Range	16–43	2–25	95–160/60–100	2–395	6.3–17.5	−3.6 to −7.5

*Normal level ± 2S.D., 2 to 27 mg/24 hrs.

tion regimen. In the Oslo study, after two months of home blood glucose monitoring, the 45 patients were randomized into the following groups: conventional treatment (15 patients), multiple insulin injections (15 patients), and continuous subcutaneous insulin infusion (15 patients). In the World Health Organization study, which was a crossover study, 25 patients received conventional treatment and 27 began a regimen of continuous subcutaneous insulin infusion.

Of the two patients described here, the woman in the Oslo study (Patient 1[15]) was 22 years of age and had had diabetes for 11 years; the patient in the World Health Organization study (Patient 2) was 19 years old and had had diabetes for four years (Table). Both patients were emmetropic, with a visual acuity of 20/20 in both eyes.

To evaluate the severity of the retinopathy, 30-degree standard color photographs were taken of both eyes by centering the exposures at one-half the distance between the fovea and the temporal edge of the optic disk. Additional photographs were taken to cover most of the remainder of the retina. According to the study

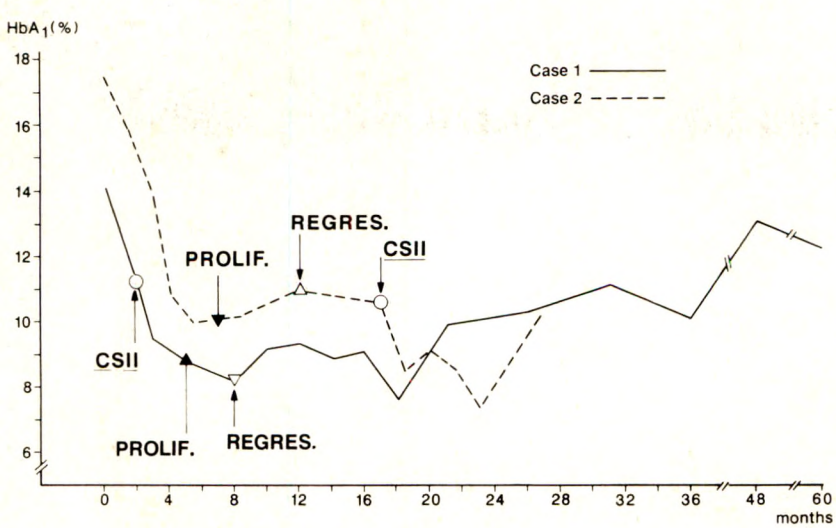


Fig. 1 (Rosenlund and associates). Level of glycosylated hemoglobin in two patients who developed florid proliferative retinopathy (Prolif.). In both patients, significant regression (Regres.) occurred three to seven months later. CSII, continuous subcutaneous insulin infusion.

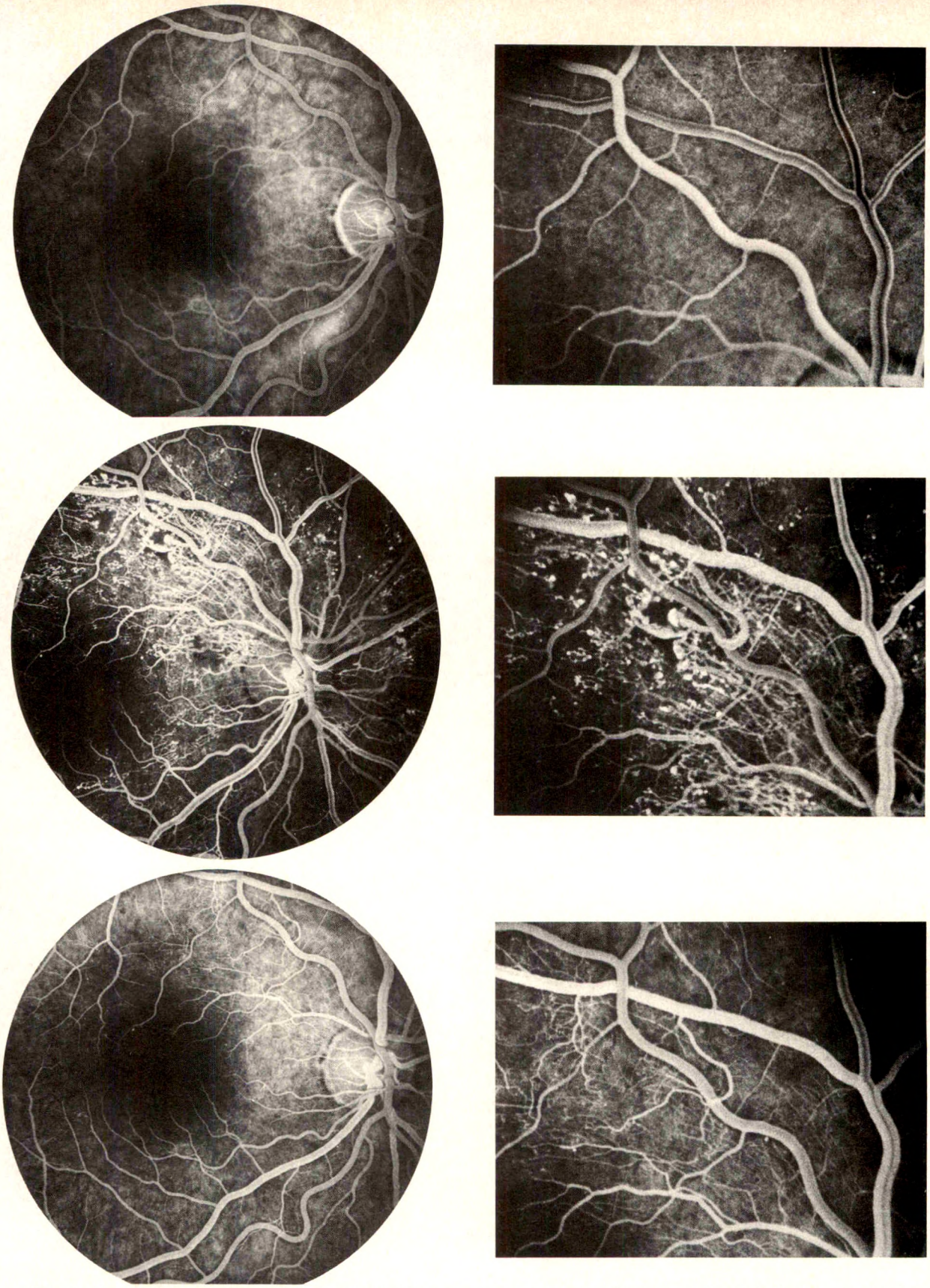


Fig. 2 (Rosenlund and associates). Patient 1. Fluorescein angiograms of transient florid diabetic retinopathy. Top left, Right fundus at the start of continuous subcutaneous insulin infusion. A few microaneurysms are present and fluorescein leakage is seen between the lower temporal artery and vein. Top right, Arcade area above the optic disk. Middle left and right, After three months of intensified insulin treatment. Note irregularities of caliber of retinal vessels, dilated veins and capillaries, endothelial buds, increased number of microaneurysms and hemorrhages, and occluded arterioles. The nonperfused capillary areas seen in the upper left region of the middle right photograph correspond to areas with soft exudates shown in Figure 3. A preretinal newly developed vessel is seen near the optic disk (middle left). Bottom left and right, Regression of retinopathy three months later. The patient continued to receive continuous subcutaneous insulin infusion.

protocols, fluorescein angiography was performed initially in one eye in all 45 patients in the Oslo study and in patients with diabetes for seven years or more in the World Health Organization study. Patient 1 initially had eight microaneurysms or hemorrhages, whereas no retinopathy was found initially in Patient 2.

The metabolic control was estimated by the level of glycosylated hemoglobin (the agar gel electrophoresis method with a normal range ±2 S.D. of 5.4% to 7.6%).[16] In both patients, home monitoring of blood glucose was introduced at the beginning of the study. The mean blood glucose values were based on weekly sampling before and 90 minutes after each meal, at bedtime, and in the morning by a filter-paper method.[17]

After a scheduled preperiod of two months, Patient 1 began continuous subcutaneous insulin infusion. This regimen was sustained throughout the five-year study period. In Patient 2, continuous subcutaneous insulin infusion was planned after six months of conventional treatment and home blood glucose monitoring. However, because proliferative retinopathy developed, continuous subcutaneous insulin infusion was postponed; it was finally introduced after 17 months. Continuous subcutaneous insulin infusion was continued for six months, after which time she administered four to six insulin injections per day.

Results

The 45 patients in the Oslo study and the 52 patients in the World Health Organization study have now been followed up for a mean of 56 months (range, 46 to 64 months) and 28 months (range, 16 to 32 months), respectively. Transient developments of soft exudates were found in 15 subjects in the Oslo study[5] and in two subjects in the World Health Organization study in the first six months. Proliferative retinopathy, except in the two patients described here, has not been noted in either study. In Patient 1, color fundus photographs of both eyes and fluorescein angiograms of the right eye were taken after two months (the start-up period) and at three, six, 12, 18, 24, 36, and 60 months. In Patient 2, color fundus photographs were taken ten times and fluorescein angiograms six times during the two-year follow-up period.

A significant decrease in the glycosylated hemoglobin level was found during the first five to six months in both patients (Fig. 1 and Table). In contrast to the other patients in the two studies, both of our patients had an initially high glycosylated hemoglobin level, which then decreased significantly.

Both of our patients were somewhat younger and had had diabetes for a shorter period of time compared to the average study participant (Table). Patient 1 had the highest level of urinary albumin in the Oslo study and Patient 2 had the second highest level in the World Health Organization study.

After five to seven months of improved metabolic control, proliferative retinopathy developed in both eyes in Patient 1 (Figs. 2 and 3) and in Patient 2 (Figs. 4 and 5). Soft exudates, irregularities of caliber of arteries and veins, capillary dilations, endothelial bud formations, nonperfused capillary areas, and neovascularization close to and on the optic disks were seen. No change in visual acuity was found. Photocoagulation was considered, but frequent ocular examinations showed regression of the retinopathy over the next three to five months (Figs. 1 through 5). The follow-up examinations at five years in Patient 1 (Fig. 3) and at two years in Patient 2 (Fig. 5) showed mild background retinopathy, although remnants of diseased retinal vessels were seen in Patient 2.

No changes in retinopathy were observed throughout an uncomplicated pregnancy and delivery of a healthy child in Patient 1 between the third and fourth years of continuous subcutaneous insulin infusion.

Discussion

An increasing number of reports suggest that progression of diabetic retinopathy may occur as a response to rigorous tightening of glucose control.[1-5,9,11,18,19] As occurred in this study, florid proliferative retinopathy has been previously described in diabetic patients with poor metabolic control.[2,9] The worsening was observed in our two patients after five and seven months of intensified insulin treatment. The increased metabolic control was achieved by home blood glucose monitoring and continuous subcutaneous insulin infusion in one patient and by conventional treatment in the other. Our study gives circumstantial evidence that a causal relation exists between a large decrease in the level of blood glucose and proliferative retinopathy.

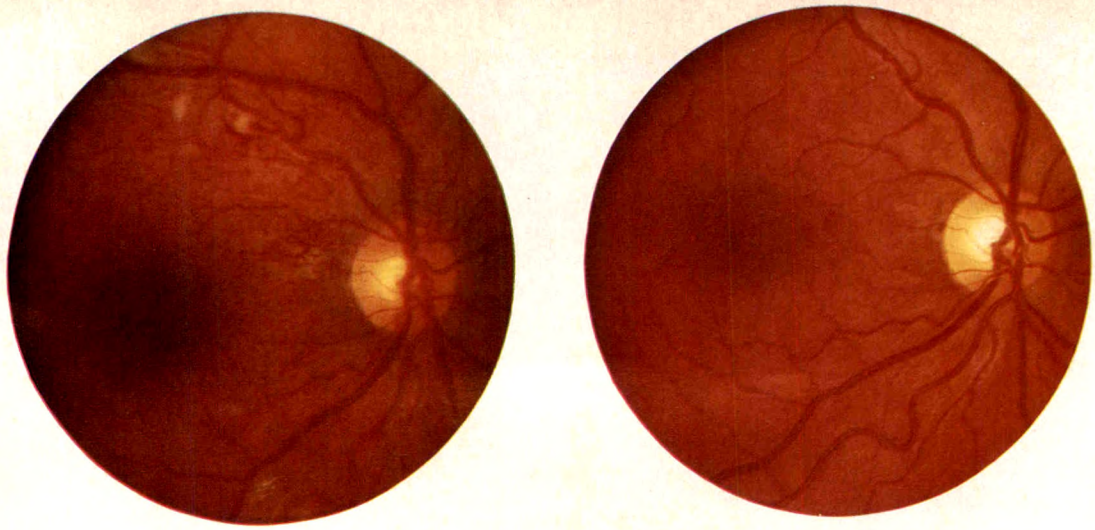


Fig. 3 (Rosenlund and associates). Patient 1. Central retina of the right eye six months after the start of the study (left) and after five years of continuous subcutaneous insulin infusion (right).

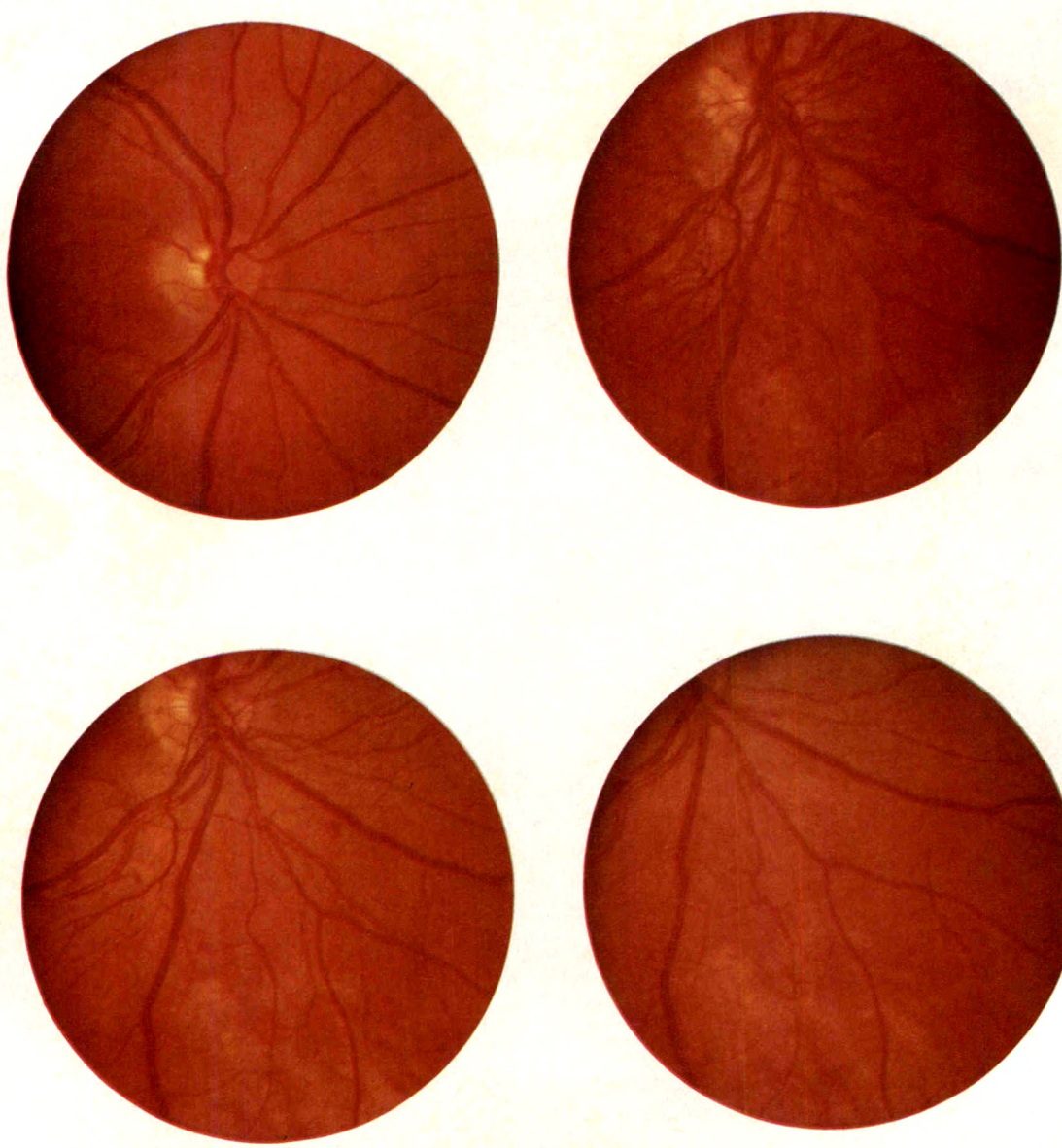


Fig. 4 (Rosenlund and associates). Patient 2. Top left, Right fundus at the start of the World Health Organization study. Top right, Proliferative retinopathy on and around the optic disk after seven months of home blood glucose monitoring. Bottom left, Six months later note regression of proliferations after continued improved metabolic control. Bottom right, Twenty months later no retinopathy was observed.

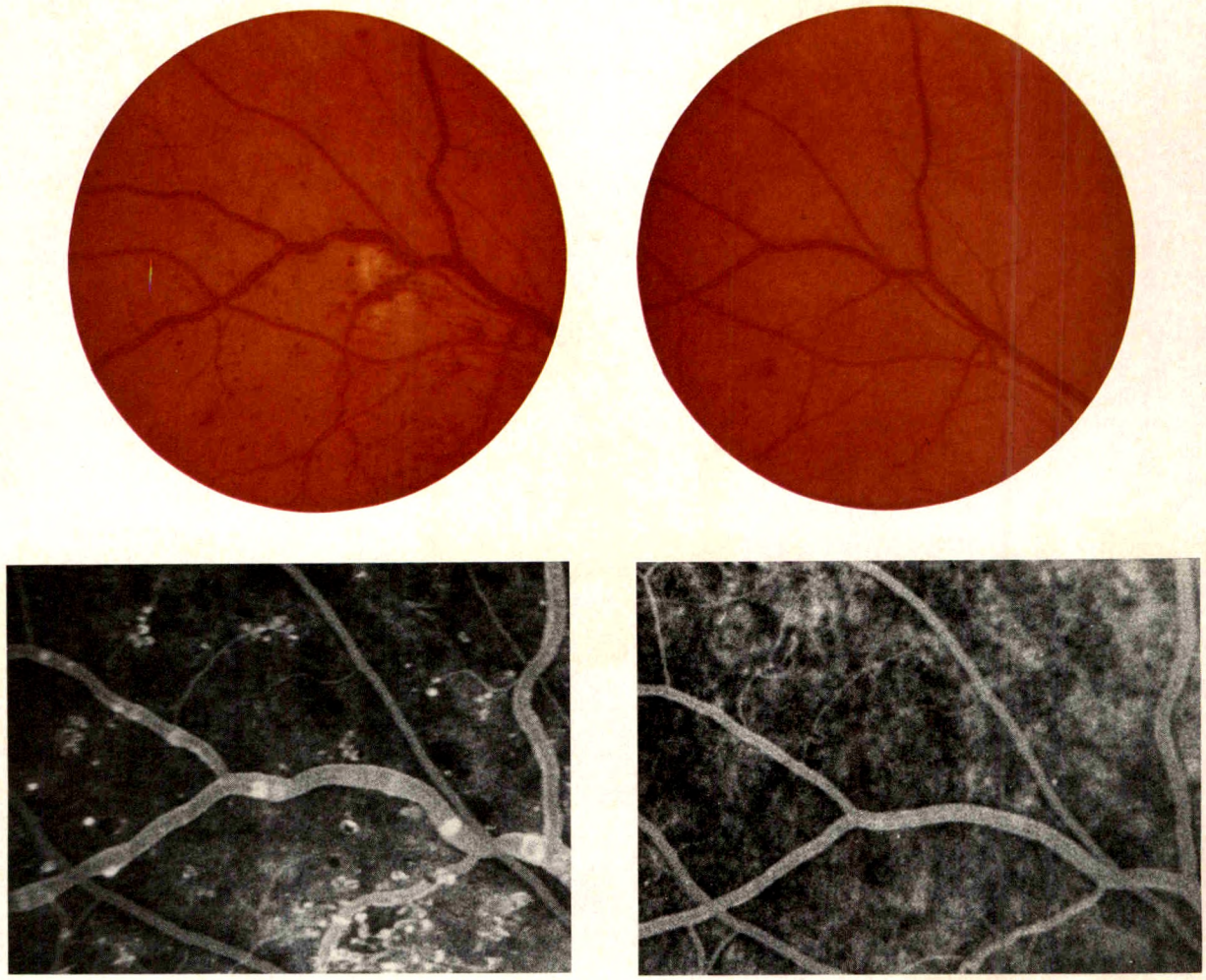


Fig. 5 (Rosenlund and associates). Patient 2. Color photographs and fluorescein angiograms showing vascular changes at eight months (left) and their regression at 16 months (right). Left top and bottom, Note venous vasodilation, beading, endothelial buds, microaneurysms, hemorrhages, and nonperfused capillary areas (soft exudates). Right top and bottom, The various lesions have significantly regressed.

The prospective nature of the Oslo and the World Health Organization studies made it possible to demonstrate the background character (high level of glycosylated hemoglobin) and response to good metabolic control (large decrease in the level of glycosylated hemoglobin) in our two patients, compared to a control group of 95 fellow diabetic patients.

We may speculate whether the high level of glycosylated hemoglobin at the start of the study or the rapid and large decrease in blood glucose level during the initial phase of the study, or both, represent the most important risk factors. Since normoglycemia represents a lower limit for a physiologic blood glucose level, it follows that a large decrease in that level is possible only in patients with initially poor metabolic control. However, further lowering of the blood glucose level may occur in insulin-dependent diabetics, and hypoglycemia may also contribute to the worsening of the retinopathy.[5,20] Reduced retinal metabolism and oxygen deprivation are likely to occur during hypoglycemic episodes, and retinal ischemia may trigger the development of neovascularization. A significant increase in frequency of hypoglycemia was noted in Patient 1.[5]

Long-term studies show that poor glycemic control is associated with a risk of developing proliferative retinopathy.[21,22] The oscillations in blood glucose level may be a significant risk factor, even more so than the high blood glucose level itself. Although no prestudy data exist on the two patients, we assume that both had a history of poor metabolic control. It is unlikely that proliferative retinopathy would have developed in our two patients, simply by chance, five to seven months after they were

included in the two studies. Rather, it was probably a result of a change in the previous steady state of high glucose metabolism. In support of this hypothesis, proliferative retinopathy is rarely noted during the first ten years after the onset of diabetes.[21,23,24] Patient 2 developed proliferative retinopathy even though she had had diabetes for less than five years. It is of particular note that both patients who developed proliferative retinopathy initially had microalbuminuria. Microalbuminuria is considered a marker of later development of serious retinopathy.[25]

Florid retinopathy is characterized by rapid development of capillary nonperfusion, microvascular abnormalities, intraretinal new vessels, and vascular proliferations from the optic disk.[26] As in Patients 1 and 2, it usually occurs in young patients with poor metabolic control and often with only minimal background retinopathy.[27] According to the most accepted view today, our patients should have undergone photocoagulation. Untreated florid retinopathy may have a bad prognosis.[27] Furthermore, the retinopathy in both of our patients would have been defined as having high-risk characteristics by the Diabetic Retinopathy Study group.[10]

However, to the best of our knowledge, our two patients benefited from the continued good metabolic control without photocoagulation. Loss of visual acuity and constriction of peripheral visual field are well-known side effects of photocoagulation.[10] With increased experience, the list of complications from photocoagulation now includes large hemorrhages, macular edema, ischemic optic neuropathy, formation of chorioretinal neovascular membranes, and retinal detachment.[28]

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OPHTHALMIC MINIATURE

However, little by little, whether some distant air holes sent a little floating light into this opaque mist or his eyes became accustomed to the obscurity, some dim vision came back to him, and he again began to get some confused perception, now of the wall he was touching, and now of the arch under which he was passing. The pupil dilates in the night, and at last finds day in it, even as the soul dilates in misfortune, and at last finds God in it.

Victor Hugo, *Les Miserables*
New York, New American Library, 1987, p. 1278

Corneal Fistulas and Their Management

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We reviewed three representative cases of chronic corneal fistula formation and provide a systematic approach to the assessment and therapeutic alternatives for this problem. In two of our patients, the fistula was managed surgically. The third patient developed endophthalmitis, which resulted in loss of light perception. Chronic corneal fistulization is a rare clinical entity resulting from malapposition of corneal tissue after traumatic, surgical, or infectious perforation. Fistulas may result in prolonged or recurrent hypotony, peripheral anterior synechia formation, or endophthalmitis. Accurate assessment of the risks associated with corneal fistula formation takes into account the type of fistula, its location in the cornea, and the condition of the ocular adnexae. We reviewed the risk factors that will determine the urgency and type of therapy used.

CORNEAL PERFORATIONS resulting from trauma or infection are a serious but relatively common problem. However, corneal fistulization, in which there is a chronic communication between the anterior chamber and the corneal surface, is a rare phenomenon that is difficult to manage. Herein we describe three representative cases of corneal fistulas and then review the problem systematically in order to highlight the difficulties these fistulas pose for the physician and to provide guidelines for effective management.

Case Reports

Case 1

A 70-year-old man was referred for management of a failed corneal graft with a chronic aqueous-draining fistula. The patient's history was notable for recurrent bouts of herpetic keratitis in the left eye necessitating corneal transplantation at age 48 years. The graft failed after one year and a second penetrating keratoplasty was performed. Eleven years later, at age 59 years, he developed iritis and glaucoma and a third keratoplasty was performed in combination with a glaucoma filtering procedure. Over the ensuing nine years, the patient developed a cataract and at age 68 years he underwent extracapsular cataract extraction with posterior chamber lens implantation. One year later, the corneal graft decompensated and a fourth corneal transplant was performed. At the time of suture removal from this fourth graft, he developed a fistulous track in the graft-host interface temporally (Fig. 1, top); the fistula drained aqueous humor chronically over a period of 18 months.

Visual acuity was R.E.: 20/20 and L.E.: counting fingers at 3 feet. The cornea and conjunctiva of the right eye were normal. There was mild conjunctival hyperemia on the left. No conjunctival filtering bleb was noted. In the left cornea, there were 6.0- and 7.5-mm diameter graft wounds, with marked edema of both the host tissue and the outer graft ring. The central graft was mildly edematous. At the temporal margin of the inner graft, there was a cystic mass with central pigmentation that tested Seidel-positive without pressure on the globe (Fig. 1, bottom left). The anterior chamber was formed, but a slight nasal shallowing and peripheral anterior synechiae were present. There was a superior iridectomy and a well-positioned posterior chamber intraocular lens with moderate posterior capsular opacification. Intraocular pressure was 14 mm Hg in both eyes. Ophthalmoscopy showed no posterior pole abnormalities.

A fifth penetrating keratoplasty combined with trabeculectomy was performed in the left eye with excision of the fistulous track. The postoperative course was uncomplicated, and after a YAG laser capsulotomy, visual acuity was correctable to 20/70 (Fig. 1, bottom right).

Case 2

A 50-year-old woman was referred for management of a long-standing corneal filtering

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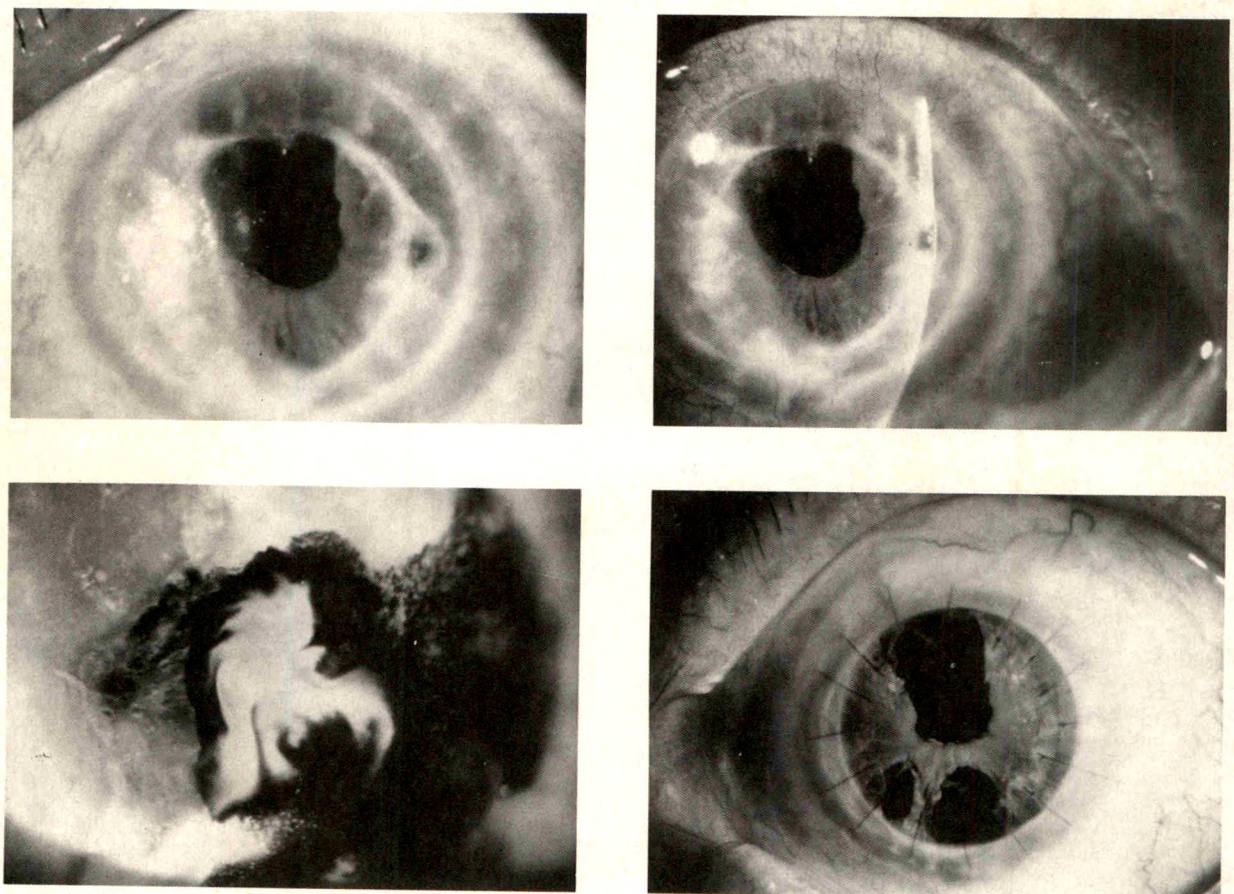


Fig. 1 (Mannis, Ruben, and Wedemeyer). Case 1. Top left, Cystic opening of the fistula at the corneal surface on the temporal side of the inner graft-host interface. Top right, Slit-lamp view of the cyst and fistulous track. Bottom left, Positive Seidel test demonstrating chronic fluorescein leakage. Bottom right, Clear graft after repeat keratoplasty and excision of the fistula.

bleb. As an infant, she had developed infectious keratitis resulting in bilateral perforating corneal ulcers. The right eye was enucleated in childhood. The left eye had developed a cystic corneal filtering bleb. She subsequently underwent an optical iridotomy and an intracapsular cataract extraction with improvement of visual acuity to 20/70.

On initial examination, best corrected visual acuity was L.E.: 20/70. There were no signs of ocular inflammation. A large cystic filtering bleb was noted in the inferior cornea, with the internal fistula evident (Fig. 2). Results of Seidel testing were negative. The anterior chamber was deep and quiet. The pupil was horizontally oval and there was an adherent leukoma near the filtering bleb. Results of ophthalmoscopy were normal. Applanation pressure was 12 mm Hg.

Two days before admission, she complained of redness and mattering of the left eye and was noted to have a mucopurulent discharge. She was treated with topical tobramycin and erythromycin for presumed bacterial conjunctivitis. On the morning of admission she awoke with significant pain, photophobia, and markedly decreased vision. At that time visual acuity was counting fingers at 3 feet. Eyelid edema and mild conjunctival hyperemia were noted. The corneal bleb was surrounded by infiltrate and was Seidel-positive. Leukocytes were present in the anterior chamber. There was a fibrinous reaction in the anterior vitreous and the red reflex was markedly diminished. A pars plana vitrectomy was performed, at which time aqueous and vitreous humor cultures were taken, and the patient received intravitreal vancomycin, gentamicin, and dexamethasone. Cultures of the vitreous and aqueous humor were positive for *Haemophilus influenzae*. Despite contin-

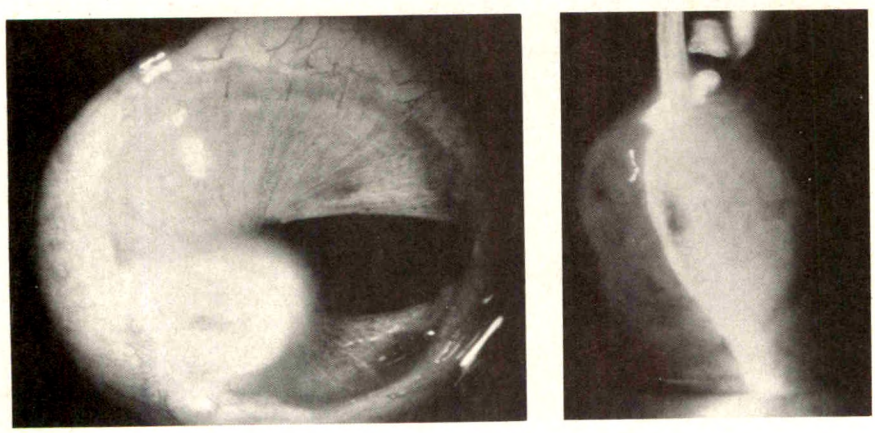


Fig. 2 (Mannis, Ruben, and Wedemeyer). Case 2. Left, Closed fistula near the inferior corneoscleral limbus. Right, Slit-lamp view of the cyst and fistulous track.

ued treatment with topical and intravenous gentamicin and cefazolin, the patient's clinical course deteriorated necessitating an excisional penetrating keratoplasty and repeat vitrectomy. The infection was controlled; however, subsequent development of an epiretinal membrane and recurrent retinal detachment resulted in permanent visual loss to the level of light perception.

Case 3

A 49-year-old man was referred for examination and management of a chronic corneal perforation in the left eye. He had had bilateral severe blepharoconjunctivitis for several years, with trichiasis and inferior punctate epithelial keratitis. This had been treated intermittently with topical gentamicin. Two months before examination, he developed a small inferior corneal perforation, with shallowing of the anterior chamber. He was treated with a bandage contact lens, topical gentamicin, and oral tetracycline. Although the chamber depth returned to normal, he developed a chronic leak at the site of the perforation.

On examination visual acuity was R.E.: 20/25 and L.E.: 20/40. The eyelid margins were hyperemic and there was significant inspissation of the meibomian glands. A left upper eyelid trichiasis was present. There was mild conjunctival injection, which was most marked in the interpalpebral space. A superior pannus, fine inferior punctate epithelial keratitis, and a ground glass central anterior stromal scar were present in the right cornea. In the left cornea, there was perilimbal vascular engorgement, paracentral punctate epithelial keratitis, and a large inferior paracentral intrastromal cyst that was Seidel-positive for multiple small leaks (Fig. 3, left). There was stromal vascularization from the inferior corneoscleral limbus to the site of the cyst. In both eyes, the anterior chamber was deep and quiet, and the iris and lens were normal. Intraocular pressure was R.E.: 16 mm Hg and L.E.: 8 mm Hg. Results of ophthalmoscopy were normal. There were numerous facial pustules as well as axial facial flush and telangiectasis. The clinical diagnosis was acne rosacea blepharoconjunctivitis. The patient was treated with oral tetracycline and underwent an uncomplicated lamellar patch graft with return of visual acuity to 20/25 (Fig. 3).

Discussion

A fistula is defined as an abnormal communication between an internal organ and the body surface. A corneal fistula is a chronic, established communication between the anterior chamber and the corneal surface. An open fistula may be defined as a track through which aqueous humor has free access to the corneal surface and tear film. A closed fistula is similarly a track to the surface of the cornea, but it is closed at the external end and there is no access to the tear film. Such fistulization can occur after trauma or corneal ulceration with perforation and poor apposition of the stromal tissue separated by the initial injury. Percolation of aqueous humor through the unhealed stromal wound may produce a cystic space bounded anteriorly by the corneal epithelium. The epi-

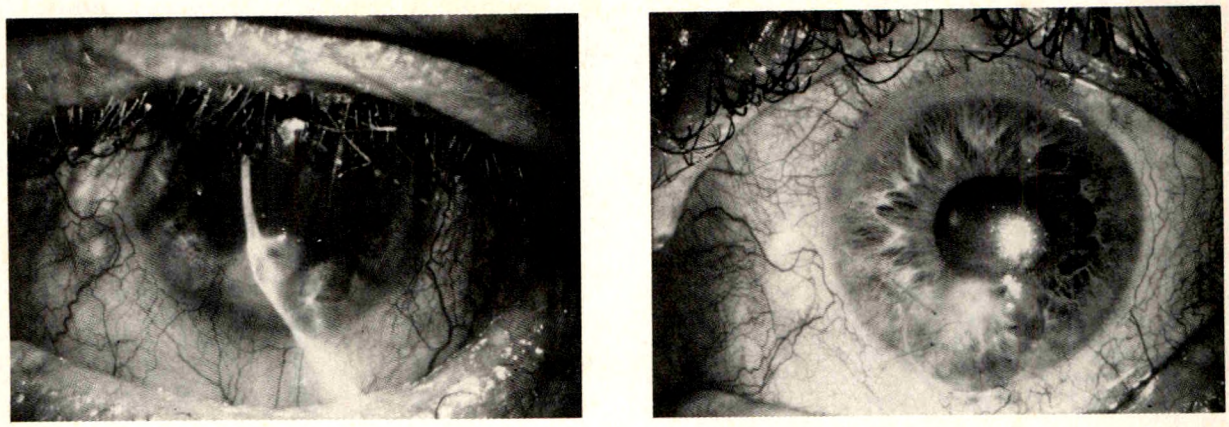


Fig. 3 (Mannis, Ruben, and Wedemeyer). Case 3. Left, Open fistula with leaking cyst at the corneal surface. Right, Lamellar keratoplasty performed for closure of the fistula.

thelial bleb that is formed may leak constantly or recurrently until the defect closes. Alternatively, if epithelium gains access to and lines the drainage track, a chronic fistula may be formed. Leakage from such a chronic fistula may correspond to an increase in intraocular pressure, draining when the pressure goes up and closing again when the pressure is relieved.[1] The cases presented herein represent examples of the rare occurrences of chronic open (Cases 1 and 3) or closed (Case 2) fistulas.

In most citations in the ophthalmic literature, "fistula" and "perforation" are used synonymously. Of the reports of chronic corneal fistulas, most are described either in the context of complicated cataract surgery with fistulization at the corneal incisional site and associated epithelial downgrowth or the intentional fistulas resulting from glaucoma filtering surgery. Duke-Elder and Leigh[1] refer to "cystoid cicatrix and fistula," in which the healing of a corneal defect is complicated by the incarceration of iris inhibiting scar formation. The loosely arranged tissue coupled with a constant flow of aqueous humor allows for the formation of a stromal cystoid space and corneal ectasia. The ectatic corneal tissue cannot withstand intraocular pressure and aqueous humor continues to seep through the defect. Such circumstances favor the downgrowth of epithelium into the fistulous track, preventing complete cicatrization and closure. Czermak[2] described the clinical and histopathologic appearance of such fistulas in detail and pointed out that an adherent iris is an almost constant feature in the circumstances of such fistula formation.

Chronic corneal fistulas have also been described as a rare complication of keratoplasty,[3,4] cataract extraction, corneal ulcer, poor resuturing of corneal wounds,[4] Terrien's marginal degeneration,[5] and more recently, keratoconus with hydrops.[6] In all of these diverse circumstances, there was a perforation site that would not heal because of the combination of poor tissue apposition and persistent aqueous humor flow.

The management of a corneal fistula depends upon the risk factors involved. The type and location of the fistula as well as the state of the ocular adnexae appear to be the most important variables. An open fistula, with aqueous humor leaking to the corneal surface and tear film, is at high risk for complications resulting from prolonged hypotony, peripheral anterior synechia formation, and most seriously, endophthalmitis. These were the primary concerns in our Cases 1 and 3. A closed fistula is of less concern in this regard. Epithelial downgrowth was not evident in any of our cases. So few cases of this entity are well documented that the risks of epithelial downgrowth are not known. One would surmise that this complication is a distinct possibility in such cases, given the histopathologic demonstration of epithelium into the fistulous track.[2] The location of these fistulas away from the conjunctiva, however, may alter the incidence of downgrowth.

The location of the fistula on the cornea may also be important. Fistulas near the inferior corneoscleral limbus may be at greater risk for bacterial contamination because of their proximity to the contents of the inferior fornix and

eyelid margin, where bacterial contaminants are most common. In our Case 2, a closed fistula near the inferior corneoscleral limbus remained intact for many years without surgical intervention. Surgery was deferred because the patient was doing well functionally and did not wish to risk surgery on her only eye. Additionally, there was no evidence of leakage. Despite this, the eye was lost to endophthalmitis from *H. influenzae*, an organism that has more frequently been associated with eyes that have filtering blebs.[7] This endophthalmitis presumably occurred through bacterial penetration at the fistula site. The vulnerability of such a closed fistula in the context of infectious conjunctivitis is emphasized by this outcome.

Finally, the condition of the ocular adnexae should be considered when determining the urgency of intervention. The presence of periocular skin disease, chronic blepharitis, entropion, ectropion, or trichiasis heightens the potential risks and may signal the need for more aggressive intervention.

Therapy of corneal fistulas include a variety of approaches. Historically, they have been treated with ocular hypotensive agents, chemical cauterization with iodine or trichloroacetic acid, diathermy,[4] cryoapplication, thermokeratoplasty,[6] conjunctival flap,[8] and lamellar or penetrating keratoplasty.[9-14]

Current recommendations for therapy will depend largely upon the specific fistula type and location. Open fistulas require prompt intervention. A superiorly located fistula in an eye with normal adnexae can be treated conservatively with topical or systemic hypotensive agents to diminish the flow of aqueous humor and to promote closure of the tissue defect. A bandage contact lens may also serve as a temporary measure to cap the fistula and maintain the anterior chamber; such a lens should be closely monitored, because of the risk of infection. Prophylactic antibiotic therapy is indicated until the fistula is permanently closed. Cyanoacrylate tissue adhesive may be used and may provide the lattice work on which healing can take place once the flow of aqueous humor is stopped.

If these measures do not succeed in promoting closure of the fistula, lamellar keratoplasty is indicated. This is most effectively performed by suturing a full or ¾ thickness corneal button into a small lamellar bed, providing tight occlusion of the fistulous track (Fig. 3). Alternatively, localized penetrating keratoplasty with complete excision of the fistula can be performed (Fig. 1, bottom left). The presence of an inferiorly located fistula, open or closed, warrants surgical intervention as a primary mode of therapy because of the high risk of endophthalmitis.

In a fistula in which there has been a chronically or recurrently shallow anterior chamber, concomitant prophylactic glaucoma surgery may be indicated at the time of fistula closure. In such cases, the fistula may have served as a filtration site that is lost at the time of closure. The presence of a normotensive eye in the presence of a Seidel-positive fistula should alert one to the possibility of a pressure increase after the fistula is closed.

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OPHTHALMIC MINIATURE

A child, six months old, was brought to the Infirmary with congenital cataracts, the lentes being the seat of the disorder; the capsules free. The child was very reluctant and vociferous; and as there was no prospect of his ceasing to cry, I introduced the needle through the sclerotic coat and lacerated a single lens. Whilst thus freely the needle was playing in the eye, the child fell asleep, soundly asleep, and so was completed the manipulation. Some time after I operated on the other eye, when, to the admiration again of the spectators and pupils, the same events occurred: again the infant fell soundly asleep, whilst the breaking up of the opacified lens was effected.

Robert Hull, "Cursory Notes" in *The Morbid Eye*
London, Longman, Orme, Brown, Green, and Longman, 1840

Infected vs Sterile Corneal Infiltrates in Contact Lens Wearers

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We examined 50 patients to determine whether differences exist between the initial clinical signs and symptoms associated with infected vs sterile corneal infiltrates. A detailed history regarding contact lens use and ocular symptoms was taken, after which a careful slit-lamp examination was performed. The ocular findings were correlated with the results of corneal cultures. Increased pain ($P < .001$), discharge ($P < .0001$), epithelial staining ($P < .0001$), and anterior chamber reaction ($P < .0001$) were associated with infected ulcers. Sterile infiltrates were usually smaller; multiple or arcuate; and without significant pain, epithelial staining, or anterior chamber reaction.

CORNEAL ULCERS are the most serious complication associated with contact lenses.[1-14] Corneal infiltrates in contact lens wearers may be infected or sterile. Decisions regarding the need to perform corneal scrapings for smears and cultures and to initiate broad-spectrum fortified antimicrobial therapy will depend on the clinical impression of the nature of the infiltrate. We designed this study to determine which clinical symptoms and signs were important in predicting whether a corneal infiltrate was infectious or sterile. This information is helpful in determining the optimal initial therapy of contact lens-associated corneal ulcers.

Subjects and Methods

We performed a prospective study on patients with untreated corneal infiltrates and a history of contact lens wear who were seen in the Emergency Room or by the Cornea Service at our institution from Aug. 1, 1986, to May 31, 1987. A complete history regarding the type of contact lens, method and frequency of disinfection, and pattern of lens use before the onset of symptoms was taken. The nature and severity of ocular symptoms were also recorded. A thorough slit-lamp examination was performed, with documentation of epithelial stain, size of the infiltrate, extent of surrounding corneal edema, and degree of anterior chamber reaction. Extensive corneal drawings were made. To standardize the history taking process and examination, all patients were seen by one of two of us (R.M.S. or T.E.C.). The laboratory studies included standard corneal smears and cultures on blood agar, chocolate, Sabouraud's, and thioglycolate media. When *Acanthamoeba* keratitis was suspected, Giemsa stains of corneal scrapings were performed and specimens including contact lenses were sent to the Centers for Disease Control for cultures whenever possible. If bacterial infection was suspected, initial therapy was topical fortified tobramycin (15 mg/ml) and cefazolin (50 mg/ml) every hour. If no infection was suspected, regular-strength tobramycin (3 mg/ml) was used four times daily because of the concern regarding an undetected early infection. The clinical signs and symptoms were correlated with the culture results and response to therapy.

Statistical analysis of the data was performed using Fisher's exact test.

Results

The study population consisted of 50 patients; there were 31 females (62%) and 19 males (38%). The median age was 29 years (range, 13 to 82 years). An initial clinical distinction was made between infected (30 of 50, 60%) and sterile (20 of 50, 40%) infiltrates (Table 1). The population consisted predominantly of

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TABLE 1
CLINICAL AND LABORATORY DIAGNOSES

	CULTURE RESULT					
CLINICAL DIAGNOSIS	POSITIVE		NEGATIVE		TOTAL	
Infected	20	(40%)	10	(20%)	30	(60%)
Sterile	0	(0%)	20	(40%)	20	(40%)
Total	20	(40%)	30	(60%)	50	(100%)

patients wearing cosmetic extended-wear soft lenses (28 of 50, 56%) or cosmetic daily-wear soft lenses (18 of 50, 36%) (Table 2).

Pain and photophobia were the most common initial symptoms. Discomfort was moderate or severe in 17 of 20 (85%) culture-positive infected cases and mild or absent in 16 of 20 (80%) culture-negative sterile infiltrates ($P < .001$) (Table 3).

On examination a discharge was present in 16 of 20 (80%) of the culture-positive infected infiltrates and absent in all (20 of 20, 100%) of the culture-negative sterile infiltrates ($P < .0001$) (Table 3). In eyes with infected infiltrates, no discharge was present in three eyes with small bacterial ulcers (less than 1 mm) and one case of *Acanthamoeba* keratitis.

The size of the corneal infiltrate was less predictive of an infectious vs sterile origin (Table 3). Although most small (0.1 to 0.9 mm) infiltrates were culture negative, seven of 20 (35%) of the culture-positive infiltrates were also small. All (five of five) infiltrates over 2 mm in diameter were culture positive. Although there were few cases, all three arcuate-shaped infiltrates were culture negative and all three ring-shaped infiltrates were caused by *Acanthamoeba* infection.

TABLE 2
CONTACT LENS TYPE AND DIAGNOSIS

	INFILTRATE			
CONTACT LENS	INFECTED	SUSPECTED INFECTED	STERILE	TOTAL
Cosmetic extended wear	9	6	13	28
Aphakic extended wear	2	0	0	2
Cosmetic daily wear	8	3	7	18
Gas permeable	1	0	0	1
Scleral	0	1	0	1
Total	20	10	20	50

An overlying epithelial defect was present in all (20 of 20) culture-positive cases and only seven of 20 (35%) of the culture-negative cases ($P < .0001$). In 13 of 20 (65%) of the culture-negative cases, there was either no epithelial defect or only superficial punctate keratitis over the infiltrate.

The amount of anterior chamber reaction also differed between those patients with culture-proven infected infiltrates and those with a negative corneal culture (Table 3). Anterior chamber reaction was absent or mild in all (20 of 20) culture-negative sterile cases and moderate or severe in most (16 of 20, 80%) of the culture-positive cases ($P < .0001$).

The suspected infected infiltrates that were proven to be culture negative were similar to the culture-positive cases with regard to ocular discomfort and the presence of an epithelial defect. However, the culture-negative infiltrates were smaller ($P < .01$) and associated with less anterior chamber reaction ($P < .01$) than the culture-positive infiltrates (Table 3). No patients had been previously treated with antibiotics.

Pseudomonas was the most frequent organism cultured and accounted for half (ten of 20) of the culture-positive cases (Table 4). In this series, *Pseudomonas* was isolated with equal frequency in extended- and daily-wear soft contact lens patients. *Acanthamoeba* infection was diagnosed in three patients wearing soft contact lenses (one case each of cosmetic daily wear, cosmetic extended wear, and aphakic extended wear).

Factors predisposing to infection were identified in eight of 20 (40%) of the patients with definite evidence of infection. Shortly before the onset of symptoms, two daily-wear soft contact lens patients slept with their lenses in place. Two patients with extended-wear contact lenses swam with their lenses in. All three patients with *Acanthamoeba* used homemade saline prepared from distilled water and salt tablets.

Two patients with *Pseudomonas* ulcers and one patient with *Acanthamoeba* keratitis lost more than two lines of vision. Two of these patients wore aphakic extended-wear lenses and one patient wore gas-permeable hard lenses. Both *Pseudomonas* ulcers were diagnosed after the patients were pressure patched for apparent corneal abrasions. Visual acuity in these patients six months after treatment of

TABLE 3
CORRELATION OF SYMPTOMS AND SIGNS WITH DIAGNOSIS

	CLINICAL/LABORATORY DIAGNOSIS					
	INFECTED/ CULTURE POSITIVE (N = 20)		STERILE/ CULTURE NEGATIVE (N = 20)		SUSPECTED INFECTED/ CULTURE NEGATIVE (N = 10)	
SYMPTOMS AND SIGNS	NO.	(%)	NO.	(%)	NO.	(%)
Pain/photophobia						
Absent/mild	3	(15)	16	(80)	2	(20)
Moderate/severe	17	(85)	4	(20)	8	(80)
Discharge						
Absent	4	(20)	20	(100)	6	(60)
Present	16	(80)	0	(0)	4	(40)
Infiltrate size (mm)/shape						
0.1 to 0.9 mm	7	(35)	14	(70)	8	(80)
1.0 to 1.9 mm	5	(25)	3	(15)	2	(20)
> 2 mm	5	(25)	0	(0)	0	(0)
Ring	3	(15)	0	(0)	0	(0)
Arcuate	0	(0)	3	(15)	0	(0)
Epithelial defect						
None/superficial punctate keratitis	0	(0)	13	(65)	0	(0)
Defect	20	(100)	7	(35)	10	(100)
Anterior chamber reaction						
Absent/mild	4	(20)	20	(100)	7	(70)
Moderate/severe	16	(80)	0	(0)	3	(30)

their ulcers was 20/70 and 20/200 because of scarring in the two eyes with *Pseudomonas* and no light perception because of glaucoma in the eye with *Acanthamoeba*.

Discussion

The initial clinical impression regarding the infectious or sterile origin of a corneal ulcer is important because it determines the diagnostic approach and subsequent therapy. Almost all lens-related infiltrates occur in patients wearing soft contact lenses. Prompt, appropriate treatment is necessary to achieve the optimal outcome and minimize visual loss in patients with microbial keratitis. We found that the initial clinical symptoms and signs were significant in predicting the origin of corneal infiltrates in contact lens wearers.

The presence of moderate pain, anterior chamber reaction, discharge, and an overlying epithelial defect were all significantly associated with a culture-positive corneal infiltrate (Table 3). Conversely, minimal pain and minimal anterior chamber reaction, absence of discharge, and epithelial staining limited to superficial punctate keratitis were factors associated with culture-negative infiltrates. Large ulcers (over 2 mm) were culture positive and small ulcers (less than 1 mm) were usually culture negative. However, one third of the culture-positive infiltrates were small. These findings suggest that all corneal infiltrates in contact lens patients associated with significant pain, anterior chamber reaction, discharge, and an overlying epithelial defect should be scraped for smears and cultures and treated as if they were infected. If these symptoms and signs are absent, it is reasonable to diagnose a probable sterile infiltrate. These can be treated with lens discontinuation, regular-strength topical antibiotics for several days, and close follow-up. Patients should not be patched.[15] All patients must be instructed to return immediately if they develop increased pain or decreased vision.

TABLE 4
ORGANISM AND CONTACT LENS TYPE

	ORGANISM				
CONTACT LENS	*PSEUDOMONAS*	*ACANTHAMOEBA*	*STAPHYLOCOCCUS EPIDERMIDIS*	OTHER†	TOTAL
Cosmetic extended wear soft	5	1	3	1	10
Cosmetic daily wear soft	4	1	1	2	8
Other*	1	1	0	0	2
Total	10	3	4	3	20

*Includes one case each of aphakic extended wear soft contact lens and gas permeable rigid contact lens.

†Includes one case each of *Staphylococcus aureus*, diphtheroid, and *Streptococcus*.

In this series the culture-negative ulcers clinically suspected to be infected were also associated with pain and an epithelial defect, but were less likely than the culture-positive ulcers to have a significant anterior chamber reaction, discharge, or size of greater than 1 mm (Table 3). Some of these ulcers probably represented sterile infiltrates. Because of the importance of early treatment of corneal infections, it is safer to overtreat some suspicious infiltrates as infected ulcers pending the results of corneal cultures rather than to risk delaying appropriate treatment. Infiltrates with some but not all of the symptoms and signs characteristic of infected ulcers should be cultured and treated as infected until proven otherwise.

Sterile infiltrates in patients wearing contact lenses have a variety of causes. Chemical reactions to preservatives in contact lens solutions can be associated with sterile infiltrates.[16-19] Hypoxia may be another factor. Peripheral infiltrates unrelated to contact lenses caused by *Chlamydia* infection and *Staphylococcus* hypersensitivity reactions can also occur in patients wearing contact lenses.

In a small number of patients in this series, the shape of the infiltrate was helpful in predicting the origin of the infection. Arcuate infiltrates were culture negative (three cases). Tight lenses may contribute to these infiltrates, and tight eyelids have been reported to cause similar-appearing infiltrates.[20] Ring infiltrates in this series were associated with *Acanthamoeba* keratitis (two cases). The diagnosis of *Acanthamoeba* keratitis in three patients during the course of this ten-month study is consistent with the recent increase in the number of cases being reported.[21-23]

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OPHTHALMIC MINIATURE

But when the squint is rather confirmed, in a lad or girl; when it is traceable to no internal nor external causation, what can be done? These cases frequently occur; and the best assumption for treatment is, that the squint is produced by local muscular weakness. If the squint be converging, assume debility of the abductor muscles. If it be divergent, assume a feeble condition of the adductores. If at one time these, at another the abducent muscles are affected, suppose a general atonic state of ophthalmic muscles. For such a condition tonics are the obvious remedy. And the external application of cold water is an admirable process.

Robert Hull, "Cursory Notes" in *The Morbid Eye*
London, Longman, Orme, Brown, Green, and Longman, 1840

The Effect of Suture Removal on Postkeratoplasty Astigmatism

Perry S. Binder, M.D.

I followed up for a minimum of six months 439 eyes that had undergone corneal transplantation using a suturing technique consisting of eight interrupted 10-0 and a single, continuous, 16-bite 11-0 nylon suture. All sutures were removed from 188 eyes an average of 20 months after surgery. After suture removal, 64 corneas had an increase of astigmatism greater than 0.5 diopter, 79 eyes showed a decrease in astigmatism greater than 0.5 diopter, and 42 corneas had no change in astigmatism. The mean astigmatism before suture removal was 3.7 diopters, and the mean astigmatism after suture removal was 3.5 diopters. There was no apparent difference in postkeratoplasty astigmatism with donor corneal diameters 0.25 to 0.75 mm greater in diameter than the recipient diameters, or with different host diseases. The longer the sutures were left in place after surgery, the smaller the quantitative change in astigmatism after suture removal. The complications of this technique were no different from other currently used suture techniques.

Excessive postkeratoplasty astigmatism is associated with poor uncorrected and best corrected visual acuity, difficult contact lens fitting, and asthenopic symptoms.[1] Since intraocular lens implantation is frequently performed at the time of keratoplasty,[2-4] it is necessary to know what corneal curvatures can be expected after keratoplasty in order to calculate appropriate lens powers. Unfortunately, excessive astigmatism and unpredictable corneal curvatures in pseudophakic transplants can lead to unexpected and unwanted refractive errors.[2,5]

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Current corneal transplant suturing techniques use interrupted sutures or a single or double continuous monofilament nylon suture[6,7] left in place 12 or more months after surgery. Spectacles or contact lenses are prescribed after the sutures are removed. The astigmatism that remains after suture removal can only be modified by relaxing corneal incisions,[8] a patterned keratotomy procedure,[9] additional compression sutures, or repeat keratoplasty. The results of relaxing incisions and patterned keratotomy procedures are unpredictable, and the procedures have potential complications.[10]

In 1979 I began a prospective, nonrandomized study to assess the effect of selected interrupted suture removal on the reduction of postkeratoplasty astigmatism.[1] Analysis of those cases[11-14] has demonstrated that the technique can reduce astigmatism effectively while sutures are in place (Table 1). The theoretical advantage of selective suture removal is that the surgeon can modify astigmatism while sutures are in place, allowing the patient to receive spectacles or contact lenses between the fifth and seventh postoperative months, well before patients are visually rehabilitated with current suturing techniques.

There are several criticisms of the technique. Extra postoperative office visits are required to remove interrupted sutures. Leaving sutures in place for extended periods could potentially lead to suture-associated bacterial corneal infection. This criticism also applies to the double-continuous suture technique.[6,7] The major criticism is that unpredictable corneal curvatures could result once all sutures are removed, producing more astigmatism than was present before suture removal. However, to my knowledge, no such study has demonstrated the effect of suture removal on astigmatism. Since March 1979, I have performed 439 transplants using the same selective suture removal technique.[1-5,11-14,19] Herein I report the effect of total suture removal on corneal astigmatism.

TABLE 1
SUMMARY OF PREVIOUSLY PUBLISHED RESULTS OF ASTIGMATISM AFTER CORNEAL TRANSPLANTATION USING OVERSIZED DONOR CORNEAS*

AUTHORS	NO. OF EYES	ASTIGMATISM† (D)	MULTIPLE SURGEONS
Davison and Bourne[6]	33	4.1	No
Insler, Cooper, and Caldwell[15]	31	3.9‡	Yes
Heidemann and associates[16]	86	5.2	Yes
Troutman, Swinger, and Belmont[17]	74	4.4–5.1	No
Foulks, Perry, and Dohlman[18]	32	3.5	Yes
Present study	188	3.5‡	No

*Donor corneas were larger than recipient corneas.

†Mean keratometry astigmatism one year or more after surgery.

‡All sutures removed.

Material and Methods

Surgical technique—All cases were performed with a double ring Flieringa ring that was attached to the episclera with four, 4-0 Dacron sutures at the 2, 4, 8, and 10 o'clock positions. A disposable trephine on a universal handle was used to delineate the diameter of the recipient cornea that was to be excised. The anterior chamber was entered with the trephine and the recipient button excised using curved corneal scissors with the blades perpendicular to the iris surface. Excessive tags of recipient Descemet's membrane were excised with curved scissors. Donor corneas with an attached scleral rim that had been preserved in McCarey-Kaufman medium or K-Sol solution were placed epithelial side down on a triple-curve Teflon block. A disposable trephine of a disparate diameter on a universal handle was then used to trephinate the donor cornea from the endothelial surface. In 1979 and 1980 a Polack punch was used. Subsequently, the technique has required two observers, 90 degrees apart, to judge perpendicularity of the trephine.

The donor cornea was sewn into the recipient over a cushion of air (and later sodium hyaluronate) using eight interrupted, 10-0 monofilament nylon sutures. In 1979 through 1984, a 6-wire needle was used; subsequently a 4-wire needle was used. The sutures were cut on the knots and the knots rotated into the recipient cornea with a Tennant tying forceps. On occasion, additional interrupted sutures were used if there appeared to be inadequate wound coaptation. A 16-bite, 16-μm suture was then used in a clockwise fashion adjacent to each preplaced interrupted suture and in between each suture. At completion of the 16 bites, a quadruple throw was made in the suture. Sodium hyaluronate was irrigated from the anterior chamber through the wound using a 27-gauge needle with balanced salt solution. Slack was then taken up clockwise from the 6 to the 12 o'clock meridian and then counterclockwise from the 6 to the 12 o'clock meridian, and the knot was tightened. The anterior chamber was reformed with balanced salt solution through the wound. If there was no evidence of a wound leak, three additional single throws were made and the suture was cut. If a wound leak was present, the process was repeated. If a wound leak persisted, additional interrupted 10-0 monofilament nylon sutures were placed at the site of the wound leak. This was unnecessary in almost all cases. A surgical keratometer was not used.

Principles of the selective suture removal technique—Both central keratometry readings and keratographs were used four or more weeks after surgery to determine which interrupted sutures were to be removed at the slit lamp.[1-5,11-14] For example, if interrupted sutures lay in the steep keratometer meridian, then one or both of the sutures were removed. In some cases, only one of the interrupted sutures was responsible for the astigmatism (Fig. 1). Sometimes the steep meridian lay between two interrupted sutures (Fig. 2). The keratograph demonstrated which sutures were to be removed. In other cases, distortion may have been produced by two sutures in only one quadrant or by multiple sutures in the same meridian on both sides of the visual axis (Fig. 3).

Moderately tight sutures produced a "D" shape to the keratograph mires, whereas extremely tight sutures totally distorted the mire pattern in that area causing the mires to bend in toward the visual axis from the suture. When the mires were distorted through rings 3 or 2 (the central rings), then suture removal was effective in reducing astigmatism. If the outer rings were distorted and the patient had little refractive or keratometer-measured astigmatism, the sutures were left in place until a subsequent visit. If all rings were equally oval

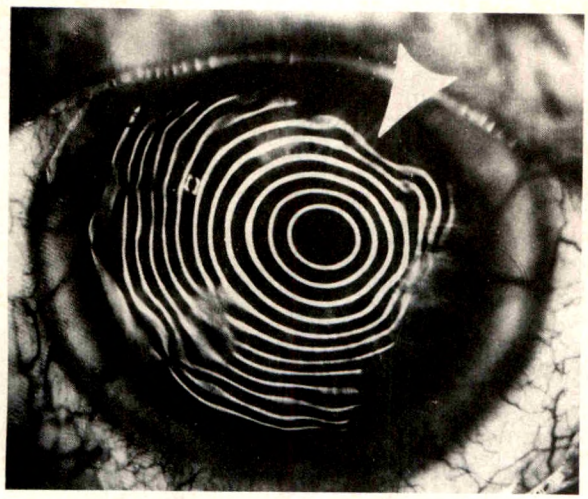


Fig. 1 (Binder). Example of one single interrupted suture producing wound compression in the same meridian as the steep keratometry readings (arrowhead).

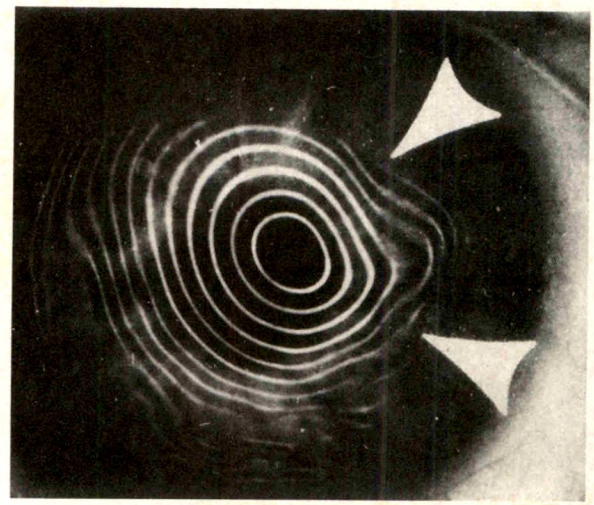


Fig. 2 (Binder). Example of two sutures in the same quadrant producing astigmatism in the meridian between interrupted sutures (arrowheads).

then suture removal usually had little effect on astigmatism, since such a pattern is produced by an oval donor or host bed, or both.

In eyes where the keratographs demonstrated significant ovality (astigmatism) but the patient had little manifest astigmatism, I removed the offending sutures in the steep meridian because my experience has shown that such eyes will subsequently manifest more astigmatism with time. Conversely, eyes with relatively round mires that had more than 3 diopters of manifest astigmatism did not undergo suture removal until the corneal topography matched the manifest astigmatism. The manifest astigmatism axis usually matched the keratograph astigmatism axis, but the amount of manifest astigmatism was usually less than that measured with the keratometer. When the axis of the manifest astigmatism did not match the keratograph astigmatic axis, I usually used the keratograph to determine which sutures should be removed. The only indication for removing sutures in an eye with less than 3 diopters of astigmatism is when the refractive error is hyperopic and corneal steepening is needed to reduce the refraction. In such cases symmetric suture removal is performed in all four quadrants.

Beginning six weeks after surgery, one or two 10-0 monofilament nylon sutures were removed at one office visit using topical proparacaine hydrochloride anesthesia. Six weeks was chosen arbitrarily as the first time sutures could be removed. Clinical experience has demonstrated they can be removed at any time after surgery but the longer sutures are left in place, the more difficult it is to pull the knot through the corneal stroma and the greater the chance the suture will break leaving a fragment of suture within the corneal stroma. A topical antibiotic drop was used before and after sutures were removed. Sutures were cut on the recipient side and the knots were pulled through the donor side to prevent suture breakage, which could leave a buried piece of suture behind or an end exposed. Sutures were removed at subsequent office visits four to eight weeks later until either the keratometry

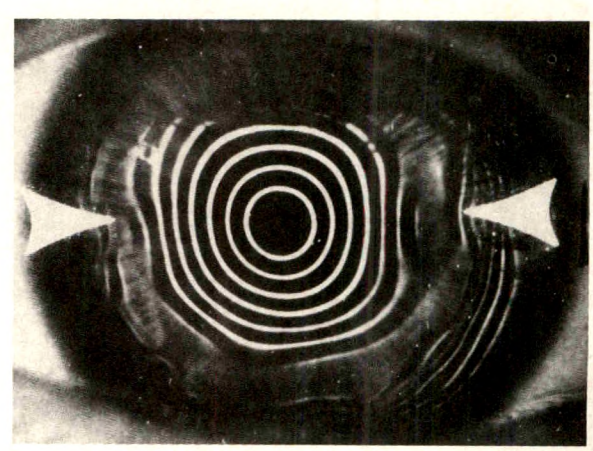


Fig. 3 (Binder). Example of interrupted suture pairs producing astigmatism in the meridian between the sutures (arrowheads).

readings stabilized, 3 diopters or less of corneal astigmatism was achieved, or until all interrupted sutures were removed. The continuous 16-μm suture and any remaining interrupted sutures were left in place. Spectacles or contact lenses were prescribed in most cases between the fifth and seventh postoperative months. Patients were then reexamined at four to six-month intervals. The 16-μm suture was removed when it spontaneously loosened or broke or after one year in those eyes with excessive astigmatism that could not be reduced by selective suture removal.

Patients were requested to return in four to eight weeks after each visit. Sometimes the astigmatism would be reduced, or there could be a new amount of astigmatism or an axis shift. In my early experience, I tried to remove more than two or three sutures in one office visit. In some cases, after removing one or two sutures the astigmatism would shift dramatically to another meridian. In other cases, I could not detect any change in astigmatism although the keratograph picture would appear less distorted. In the former circumstance, removal of more sutures in the new astigmatism axis would produce highly unpredictable results. Another axis shift might occur, and I would find myself chasing the astigmatism but not reducing it. It has since been my clinical impression that it is best to limit interrupted suture removal to one or two per session and measure the effect a minimum of four weeks later. In those cases in which I tried to remove too many sutures in one session or remove all sutures including the continuous suture before 12 to 18 months, I was unable to reduce the final astigmatism, and in some cases I actually increased the final astigmatism.

The data for this study were obtained by fellows, technicians, or myself one or more months after removal of all sutures. When patients returned for subsequent visits after total suture removal, new data replaced previous data. Statistical analysis was performed using a statistical software package.

Results

Study population—Of a total of 662 penetrating keratoplasties performed between March 1, 1979, and Oct. 1, 1986, 439 (71%) were completed using the selective suture removal technique.[1-5,11-14] Eyes not undergoing selective suture removal included those with acute corneal perforations, and severe inflammation or infection. Children who could not cooperate for in-office suture removal and some cases performed in 1979 before I switched completely to the current technique also did not receive the selective suture removal technique. Preoperatively, 47 eyes had corneal edema, 61 had keratoconus, 41 had a combination of corneal leukoma and cataract, 15 had Fuchs' endothelial dystrophy and cataract, and 24 had a previously failed graft or aphakic corneal leukoma (Table 2). Of the 439 eyes undergoing the selective suture removal technique, 188 (43%) had all sutures removed a mean of 20.3 months after surgery (range, 12 to 71 months) (Table 3). This group of eyes is the focus of this study.

An analysis of cases performed in a given year was made to evaluate what effect, if any, increased surgical experience might have on astigmatic results (Table 4). Those eyes in which the 16-μm suture was inadvertently cut (or spontaneously broke) before 12 months after surgery underwent removal of interrupted sutures after 12 months to allow time for adequate wound healing. Data were available on all eyes for analysis. None of the eyes were lost to follow-up before removal of the continuous 16-μm sutures. As of Nov. 1, 1987, 180 eyes remained in the study, with four patients lost to follow-up and four deaths. The mean post-

TABLE 2
RECIPIENT DIAGNOSIS VS POSTOPERATIVE ASTIGMATISM

RECIPIENT DIAGNOSIS	NO. OF EYES	MEAN ± S.D. POST SUTURE REMOVAL ASTIGMATISM (D)	CHANGE INTERVAL* (D)
Aphakic bullous keratopathy	26	3.6 ± 2.4	−4 to +4.9
Pseudophakic bullous keratopathy	21		
Keratoconus	57	2.9 ± 2.1	−3.5 to +1.75
Keratoconus and cataract	4		
Fuchs' dystrophy and cataract	15	3.5 ± 2.5	−4.6 to +2.9
Leukoma and cataract	41		
Leukoma, failed graft	24		

*Change in keratometer astigmatism after suture removal; range encompasses 90% of the eyes.

TABLE 3
EFFECT OF TIMING OF SUTURE REMOVAL ON POSTKERATOPLASTY ASTIGMATISM

TIME OF 16-μM SUTURE REMOVAL AFTER SURGERY (MOS)	NO. OF EYES	MEAN FINAL ASTIGMATISM (D)	CHANGE INTERVAL* (D)	MEAN CHANGE (D)
<12	43	3.3	−6.4 to +2.4	−1.25
12–18	44	3.6	−2.7 to +3.2	+0.29
18–24	43	3.5	−3.1 to +2.5	−0.34
24–32	34	3.1	−3.5 to +2.6	+0.17
>32	24	3.5	−3.9 to +4.8	−0.35
<18	88	3.4	−4.4 to +3.3	−0.48
>18	100	3.4	−3.5 to +2.8	−0.15
<24	126	3.5	−4.4 to +2.8	−0.44
>24	62	3.2	−3.6 to +4.8	−0.04
<30	150	3.3	−4.4 to +2.8	−0.43
>30	38	3.5	−3.6 to +4.8	−0.02

*Encompasses range of 90% of eyes.

operative follow-up period from the date of transplant was 42.7 months, with 108 eyes (57%) followed for 36 or more months (Fig. 4).

Of the 188 eyes in this study, seven were operated on with the same diameter trephines used on the donor and recipient, 32 were operated on with a 0.25-mm trephine diameter disparity, 64 with a 0.5-mm disparity, and 85 with a 0.75-mm disparity. The trephine sizes used ranged from 7.0 to 8.5 mm for the recipient

TABLE 4
POSTKERATOPLASTY ASTIGMATISM YEAR OF SURGERY VS ASTIGMATISM

YEAR OF SURGERY	NO. OF EYES	MEAN ± S.D. FINAL ASTIGMATISM (D)
1979	6	3.7 ± 0.6
1980	20	3.6 ± 2.8
1981	20	3.3 ± 2.1
1982	36	3.6 ± 2.4
1983	37	3.4 ± 2.2
1984	40	3.2 ± 2.2
1985	26	3.1 ± 3.0
1986	3	2.8 ± 2.8
Before 1983	84	3.4 ± 2.3
After 1983	104	3.2 ± 2.4

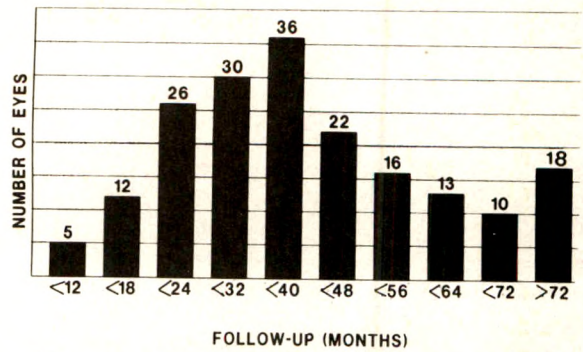


Fig. 4 (Binder). Distribution of patient follow-up after corneal transplantation. Seventy-seven percent (145 of 188) of all eyes were followed up for two or more years after surgery.

corneas and from 7.0 to 9.0 mm for the donor corneas. Thirty-seven eyes in the study were aphakic, 73 were phakic, and 78 were pseudophakic.

Complications—Six eyes had a wound leak or a clinically significant wound override on the first postoperative day, requiring a single interrupted 10-0 monofilament nylon suture repair. Three eyes had a bacterial corneal ulcer eight, 24, and 36 months postoperatively that appeared to be associated with a broken 16-μm suture. After medical therapy, visual acuity in two of these eyes returned to its original level, with the third eye losing two lines of visual acuity from 20/30 to 20/50. A wound leak that occurred after removal of a single interrupted suture spontaneously sealed. Fourteen immunologic graft rejection episodes occurred unrelated to suture removal; five developed irreversible edema. The 16-μm suture was inadvertently cut in two eyes at the time of interrupted 10-0 suture removal. In these cases, one or two loops of the 16-μm suture were cut leaving the remaining ends buried in the recipient cornea. The suture was subsequently removed as clinically indicated. The suture spontaneously untied in three other eyes and was retied without incident. Eight pseudophakic, eight aphakic, and 19 phakic eyes required contact lenses to achieve their best corrected visual acuity. Five eyes required a relaxing wound incision or patterned keratotomy for excessive astigmatism after suture removal.[10]

Astigmatism results—The mean corneal astigmatism (±S.D.) before suture removal was 3.7 ± 2.6 diopters (range, 0 to 14.6 diopters) (Fig.

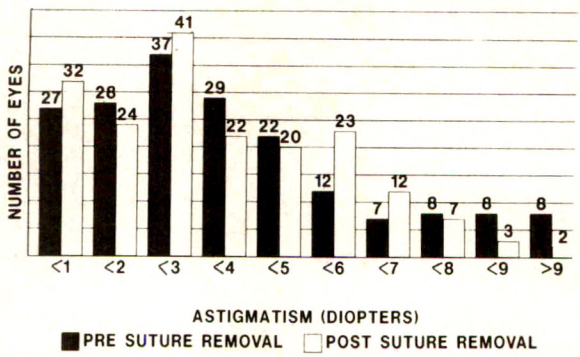


Fig. 5 (Binder). Distribution of astigmatism before and after suture removal. One hundred two eyes (55%) had less than 3.5 diopters of astigmatism before suture removal, and 104 eyes (56%) had less than 3.5 diopters of astigmatism after removal. Data were not available for two eyes.

5). The mean corneal astigmatism after suture removal was 3.5 ± 2.3 diopters (range, 0 to 10 diopters). This difference was not significant (paired *t*-test, $t = 1.496$, $P = .13$). The mean change in corneal astigmatism was −0.2 ± 2.4 diopters (Table 5). Sixty-four corneas (34%) had an increase in astigmatism of greater than 0.5 diopter (range, 0.50 to 6.25 diopters), while 79 (42%) eyes had a decrease in astigmatism of greater than 0.5 diopter (range, 0.50 to 9.6 diopters) (Table 5). If 1.00-diopter change is considered clinically significant, then 49 eyes (26%) had 1 or more diopters of increased astigmatism after suture removal.

TABLE 5
CHANGE IN ASTIGMATISM AFTER SUTURE REMOVAL (N = 186)*

CHANGE IN ASTIGMATISM (D)	NO. OF EYES
Decrease (n = 79)	
0.5–1.00	14
1.00–1.50	17
1.50–2.00	15
2.00–3.00	15
3.00–4.00	8
>4.00	10
Increase (n = 64)	
0.5–1.00	15
1.00–1.50	18
1.50–2.00	8
2.00–3.00	13
3.00–4.00	4
>4.00	6
No change	43

*Data not available for two eyes.

It has been suggested that preoperative keratometry readings may influence postkeratoplasty readings. Preoperative (keratometry-measured) astigmatism was available for 108 of 188 (57%) eyes (Table 6). Many of the excluded readings were distorted because of corneal disease (for example, edema, keratoconus), which made it difficult to measure the amount of astigmatism. Most eyes had less than 3 diopters of preoperative astigmatism. Nineteen eyes with more than 5 diopters of preoperative astigmatism had amounts of post-suture removal astigmatism similar to those eyes with less than 3 diopters of preoperative astigmatism (Table 6). Preoperative astigmatism did not predict postoperative astigmatism (multiple regression, $F = 0.34$, $P = .57$).

In an analysis of the amount of astigmatism present at the time of suture removal with astigmatism after total suture removal, 42 eyes with more than 5 diopters of pre-suture removal astigmatism (mean, 7.63 diopters) had a greater reduction in astigmatism after total suture removal compared with eyes with less than 5 diopters of pre-suture removal astigmatism (Table 7). The range of astigmatism after suture removal in the former group was 7.7 diopters (−6.70 to +1.00) for 90% of the eyes (Table 7) compared with a range of 5.25 diopters (−2.00 to +3.25) for the group of 83 eyes with less than 3.0 diopters of postoperative astigmatism.

The theory of the selective suture removal technique is based on the assumption that the corneal curvature can be modified in the early postoperative period and then allowed to remain in a given configuration for more than one to two or more years.[1,11-14] If the theory is correct, that is, the wound permitted to heal in a more round configuration, one might expect less change in astigmatism (and presumably lesser amounts of astigmatism) than if all sutures were removed early in the postoperative period. In this study, no significant difference was found in mean corneal astigmatism between groups of eyes that had all sutures removed at various postoperative time periods (Table 3) (multiple regression, $F = 2.23$, $P = .133$). However, the largest individual corneal curvature changes were found in the time period closest to surgery, which suggested that the wound was not stable. Furthermore, a smaller mean change in astigmatism was seen in the

TABLE 6
EFFECT OF PREOPERATIVE CORNEAL ASTIGMATISM ON POSTKERATOPLASTY ASTIGMATISM

AMOUNT OF PREOPERATIVE KERATOMETRY ASTIGMATISM (D)	NO. OF EYES*	MEAN ASTIGMATISM (D)	
		BEFORE SUTURE REMOVAL	AFTER SUTURE REMOVAL†
<3	68	3.73	3.34
3–5	21	3.01	2.52
>5	19	3.70	3.03

*Preoperative keratometry was not obtainable on all eyes.

†Latest readings after suture removal.

groups of eyes in which all sutures were removed before 18 months (mean change, 0.54 diopter) compared to those with sutures left in place for greater lengths of time (mean change, 0.17 diopter), although this difference was not significant (Table 3). These two findings suggest that leaving sutures in place for extended periods of time after selective interrupted suture removal has been completed will permit wound healing in an acceptable configuration. The effect of the suture slowly biodegrading over time may also have a beneficial effect on wound configuration by allowing the wound to adapt slowly to a given configuration.

Oversize donor buttons have been used widely for the last ten years because they make wound closure easier. In aphakic eyes, oversize grafts have been recommended to decrease the incidence of postkeratoplasty glaucoma.[1,20] Increasing the disparity of the donor size to the recipient size has also been expected to increase the mean corneal curvature.[15,16,21] In this series, I used a polycarbonate block to trephine donor buttons.[22] With this technique, trephines oversized by 0.75 mm in diameter tended to produce 0.5-mm oversize buttons.[21] There was no apparent effect of increasing donor/recipient disparity on astigmatism (analysis of covariance, $F = 0.162$, $P = .92$), nor was there an effect of different donor/recipient combinations on astigmatism (analysis of covariance, $F = 0.057$, $P = .79$).

Previous analysis of astigmatic results with the present technique suggested an effect attributable to the status of the lens. Phakic eyes (mean astigmatism, 2.99 diopters) tended to have less astigmatism than the other groups of eyes, but the difference was not significant (analysis of covariance, $F = 1.2$, $P = .3$).

It should be noted that if I only reported keratoconus cases (61 eyes, Table 2), I would have reported a mean astigmatism of 2.9 diopters, whereas the mean astigmatism for the entire series of 188 eyes was 3.5 diopters. Therefore, reporting a series of selected cases from an unknown, larger patient population may not provide accurate astigmatic results.

Discussion

There are many factors that may affect postkeratoplasty corneal curvature,[12] including tilt of the trephine on the donor or recipient cornea,[23] placement of an oval donor cornea in a spherical recipient opening (or vice versa),[17] an improperly fitted scleral fixation ring, eccentric location of the trephine on the donor or recipient cornea,[24] and suture pattern and technique.[1,18] Although these factors are probably important, good surgical technique can reduce their influence; selective suture removal can partially treat the astigmatism they create.

Previous studies of postkeratoplasty astigmatism using oversize donor buttons have reported the results of more than one surgeon or multiple surgical techniques (Table 1). Some studies have been retrospective and selected

TABLE 7
ASTIGMATISM IMMEDIATELY BEFORE VS AFTER SUTURE REMOVAL

PRESUTURE REMOVAL ASTIGMATISM (D)	NO. OF EYES	BEFORE SUTURE REMOVAL (D)	AFTER SUTURE REMOVAL (D)	RANGE OF CHANGE (D)	CHANGE INTERVAL* (D)
<3.0	83	1.57	2.13	−2.75 to +6.25	−2.00 to +3.25
3–5	47	3.93	3.53	−4.00 to +4.87	−4.00 to +3.50
>5	42	7.63	5.34	−9.80 to +2.60	−6.70 to +1.00

*Range encompasses 90% of the eyes.

from a larger, undescribed population of patients with corneal transplants.[25] Most of the studies have published results with some sutures in place or with less than 14 months of postkeratoplasty follow-up (Table 1). Most of the studies have reported signficant patient dropout. The present study is unique in that it reports the results of one surgeon performing the same suture and surgical technique in a prospective study with no patient dropout, and a mean follow-up period of 43 months (Fig. 4), with 78% of eyes followed up for more than two years after surgery and 58% followed up for more than three years after surgery.

This study was not randomized. It is possible that different results (better or worse) may be found in a prospective, randomized study performed by only one surgeon who uses more (or fewer) interrupted sutures with the same continuous 16-μm suture technique described herein. Because a previous analysis of my cases performed with interrupted sutures or continuous 10-0 nylon sutures before the present study demonstrated excessive astigmatism (4.57 and 6.44 diopters, respectively),[1] I did not want to use a technique that produced excessive astigmatism in my hands in order to have a group for comparison. My improved results may be a result of increased surgical experience since my original publication[1] because the astigmatism results from a concurrent group of cases performed with interrupted sutures may have been similar to the result of the current study. However, an analysis of my astigmatism results on a year-by-year basis suggests there was no difference using the same technique (Table 4) (multiple regression, $P = .479$). I chose not to use a double-continuous suture technique because when one removes the 10-0 suture from the double-continuous suture at two months,[6,7,16] the amount of astigmatism that remains cannot be changed until the 11-0 suture is removed 12 to 14 or more months later or when compression sutures are added.

Previous results of the selective suture removal technique demonstrate that it can reduce astigmatism after corneal transplantation while sutures are in place.[11-14] The advantage of this technique is to permit rapid recovery of visual acuity compared to techniques that require all sutures to be removed before a final spectacle prescription can be given. An additional benefit of the procedure is that it reduces astigmatism (Table 1). It appears that this technique is most effective when the cornea is allowed to heal in a fixed configuration. If the 16-μm suture is removed before 18 months, a greater change in astigmatism will occur compared to when sutures are left in place 18 or more months (Table 3). Therefore, based on my results, leaving sutures in place for 18 or more months appears to provide a more stable wound and less corneal curvature change after suture removal. If sutures are removed well before the wound has healed, unpredictable results may occur.

The mean corneal astigmatism reported in this study was 3.5 diopters when all sutures were removed. The mean astigmatism for the remaining 254 eyes with some interrupted sutures and the continuous suture in place was 3.0 ± 2.3 diopters (range, 0 to 11 diopters) (unpublished data). The present group of 188 eyes without sutures contains many eyes with excessive astigmatism that could not be reduced by selective suture removal and consequently underwent removal of the 16-μm suture in hopes of reducing astigmatism. This group also contains eyes in which the 16-μm suture broke spontaneously before the selective suture removal technique was complete. This group consisted of 48 eyes in 1983 (mean astigmatism, 4.9 diopters).[12] As more suture removal cases were added, it grew to 65 eyes in 1984 (mean astigmatism, 3.78 diopters),[13] and 117 eyes in 1985 (mean astigmatism, 3.4 diopters).[14] I expect the mean astigmatism to drop further as more eyes are added to this population from the present group of eyes with sutures, whose mean astigmatism is lower (3 diopters) than the group of eyes whose sutures have been removed (3.5 diopters). The technique is not a panacea, since 59 of 186 eyes (32%) had a worsening of astigmatism ranging from 0.5 to more than 4 diopters (Table 5, Fig. 5) after suture removal. Forty-eight (26%) of the eyes had an increase of more than 1 diopter after suture removal.

Although my previous suture technique with oversize grafts produced excessive astigmatism,[1] the use of the selective suture removal technique reduced the astigmatism associated with increased graft/recipient disparity.[11-14] The current technique does not appear to increase risks to the transplant compared with other techniques. Until such time as we are able to control the factors that lead to astigmatism, the technique of selective suture removal allows the corneal surgeon to provide patients with a reasonable level of astigmatism with early visual rehabilitation. These results do not preclude the possibility that one surgeon may obtain the

same or better results with a different surgical or suture removal technique. Whether or not different patterns of interrupted 10-0 sutures combined with a continuous 11-0 suture can be as effective will require additional study.

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OPHTHALMIC MINIATURE

You prefer to stand by the window? I understand. You like my little view. Have you noticed that the narrower the view the more you can see?

Walker Percy, *Lancelot*
New York, Avon Books, 1977, p. 1

A Study of Race Matching Between Donor and Recipient in Corneal Transplantation

David C. Musch, Ph.D., Roger F. Meyer, M.D., Alan Sugar, M.D., and H. Kaz Soong, M.D.

We investigated the influence of a racial match or mismatch between the corneal donor and recipient on the risk of endothelial rejection and subsequent graft failure in 998 corneal transplant recipients. Actuarial survival analysis showed no significant difference in the cumulative risk of endothelial rejection between the 676 race-matched and 322 race-mismatched recipients. Recipients who had preoperative factors that placed them at a higher risk of endothelial rejection (n = 208) also were not subject to a higher incidence of endothelial rejection if they received race-mismatched tissue. Graft failure after endothelial rejection was not found to differ among race-matched or -mismatched groups.

ENDOTHELIAL GRAFT REJECTION after penetrating keratoplasty is a frequent postoperative complication, occurring in 16% to 30% of recipients in large series with several years of follow-up.[1-3] While the rejection episode is often reversible with prompt recognition and treatment, the corneal recipient may have irreversible pathologic changes in the corneal graft resulting from an unrecognized allograft rejection, noncompliance with the prescribed treatment, or treatment-resistant endothelial rejection. The frequency of such occurrences has made endothelial rejection one of the leading causes of graft failure after penetrating keratoplasty.[1,2,4]

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While some risk factors are widely recognized, such as previous graft failure as a result of endothelial rejection and preoperative stromal vascularity,[1,2,4-6] the need for race matching between the corneal donor and recipient to reduce the incidence of endothelial rejection has not been clarified.

Studies of graft and patient survival after renal transplantation have addressed the effect of donor and recipient racial concordance. Several studies that addressed race matching between the renal donor and recipient reported an increased risk of renal graft failure among recipients receiving a kidney from a donor of another race.[7-9] Other kidney transplantation studies, however, have failed to show such an effect.[10,11]

We undertook this study to evaluate the risk of endothelial graft rejection and subsequent graft failure in recipients receiving tissue from race-matched or -mismatched donors.

Material and Methods

During a six-year period (1980 through 1985), ophthalmic information from the medical records of all patients undergoing penetrating keratoplasty surgery at our institution was entered into a computerized database (the Michigan Corneal Transplantation Patient Registry). Follow-up on these patients (n = 1,287) continues to the present time. This database was accessed for the purposes of this study.

Information on the race of the corneal donor was obtained from tissue report forms, which are completed by the personnel involved in tissue harvesting. Since the donor's race was not routinely recorded in the early 1980s, information on the donor race was available for only 1,006 (78.2%) of the penetrating keratoplasty procedures performed.

Endothelial rejection episodes were noted from the patient's medical record, which docu-

ments the clinical judgment of the attending staff, who are ophthalmic specialists in cornea and external disease. In the few cases where a referring physician noted an endothelial rejection occurrence, confirmation for the diagnosis was sought from the attending staff to whom the patient was referred.

In order to evaluate the time-related incidence of endothelial rejection in a group of patients who had variable entry and exit, and therefore variable follow-up, the product-limit (Kaplan-Meier) estimate of the cumulative survival curve was used.[12] Comparison of survival curves was performed by using the Mantel-Cox and generalized Wilcoxon tests, as generated from statistical software.[13]

Results

After excluding the few nonblack, nonwhite donors (n = 3) and recipients (n = 5), 998 cases were included in this study. Our sources of corneal donor tissue yield a donor racial distribution that is 30% black and 70% white, while our corneal transplant recipients represent a tertiary referral population that is about 5% black and 95% white (Table 1). Since tissue distribution occurs randomly, without regard to donor or recipient race, the expected and observed donor/recipient racial matches and mismatches are almost identical (Table 2). A racial match occurred in 676 (67.7%) corneal transplant surgeries, while a racial mismatch occurred in 322 (32.3%) surgeries. Most of the racial mismatches (n = 285, 88.5%) occurred when a white recipient received corneal tissue from a black donor. The two groups (race matched and race mismatched) did not differ by age, sex, preoperative stromal vascularity, or primary diagnoses (Table 3).

Endothelial rejection episodes occurred in 135 (20.0%) of the patients receiving race-matched tissue, and 63 (19.6%) of those receiving race-mismatched tissue. Since these incidence rates are influenced by variable lengths of follow-up, the cumulative risk of endothelial rejection after penetrating keratoplasty was contrasted between groups using Kaplan-Meier survival analysis techniques (Fig. 1). Survival curves for the race-matched and race-mismatched groups did not differ significantly through 36 months of follow-up (P = .98, Mantel-Cox test; P = .78, generalized Wilcoxon test).

The 208 patients (20.8%) with preoperative factors that predispose to endothelial rejection (previous graft failure or stromal vascularity) were evaluated separately to determine if racial matching of tissue was beneficial in this subgroup. Comparison of the cumulative risk of endothelial rejection in race-matched (n = 142) and race-mismatched (n = 66) high-risk recipi-

TABLE 1
RACIAL DISTRIBUTION OF DONOR AND RECIPIENT GROUPS
(N = 998)

	RACE			
	BLACK		WHITE	
GROUP	NO.	(%)	NO.	(%)
Donors	299	(30.0)	699	(70.0)
Recipients	51	(5.1)	947	(94.9)

TABLE 2
EXPECTED AND OBSERVED RACIAL MATCHES AND MISMATCHES BETWEEN DONORS AND RECIPIENTS

DONOR/RECIPIENT RACE	EXPECTED	OBSERVED
Match		
White/white	664	662
Black/black	15	14
Mismatch		
Black/white	284	285
White/black	35	37

TABLE 3
COMPARISON OF PREOPERATIVE CHARACTERISTICS IN RACE-MATCHED AND -MISMATCHED RECIPIENTS

PREOPERATIVE CHARACTERISTIC	RACE-MATCHED (N = 676)	RACE-MISMATCHED (N = 322)
Age (mean yrs)	63.5	61.0
Sex (%F)	59.0	57.8
Stromal vascularity (%)	12.1	13.1
Diagnosis (%)		
Pseudophakic bullous keratopathy	21.6	22.7
Aphakic bullous keratopathy	16.4	13.4
Fuchs' dystrophy	15.8	14.9
Keratoconus	11.1	13.7
Failed graft	10.5	10.2
Other	24.6	25.0

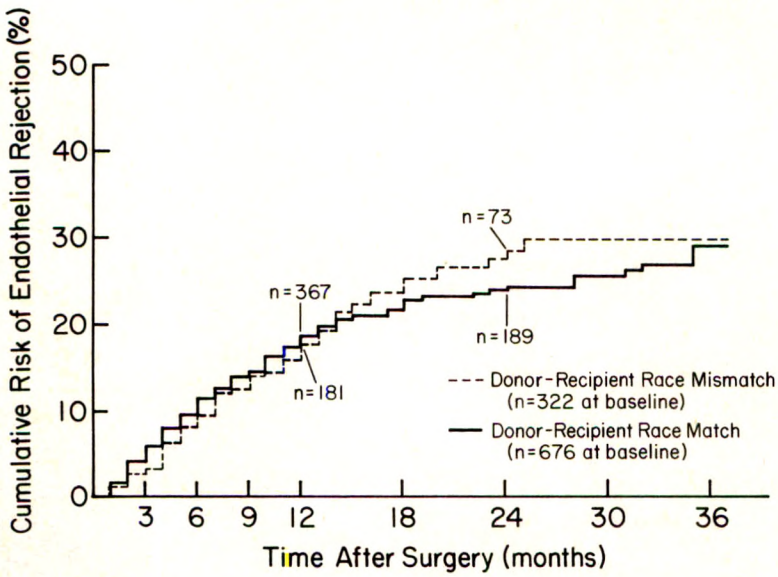


Fig. 1 (Musch and associates). Kaplan-Meier analysis of the risk of endothelial rejection after penetrating keratoplasty in race-matched and -mismatched recipients (P = .98, Mantel-Cox test; P = .78, generalized Wilcoxon test).

ents (Fig. 2) showed no significant overall difference (P = .40, Mantel-Cox test; P = .63, generalized Wilcoxon test), although further follow-up will be necessary to produce sufficient sample sizes to evaluate differences in the risk of rejection 18 months and more after surgery.

Finally, graft failure caused by an endothelial rejection episode was investigated to determine if the donor and recipient's racial makeup influenced this outcome. The overall, crude incidence of graft failure caused by endothelial rejection in those receiving race-matched tissue was 3.0% (n = 20) compared to 2.2% (n = 7) in those receiving race-mismatched tissue. Survival analysis of the time-related risk of graft failure caused by rejection (Fig. 3) showed no significant difference between groups (P = .54, Mantel-Cox test; P = .24, generalized Wilcoxon test).

Discussion

Corneal donor tissue is currently distributed without regard to the respective races of the donor and recipient. While there are no pub-

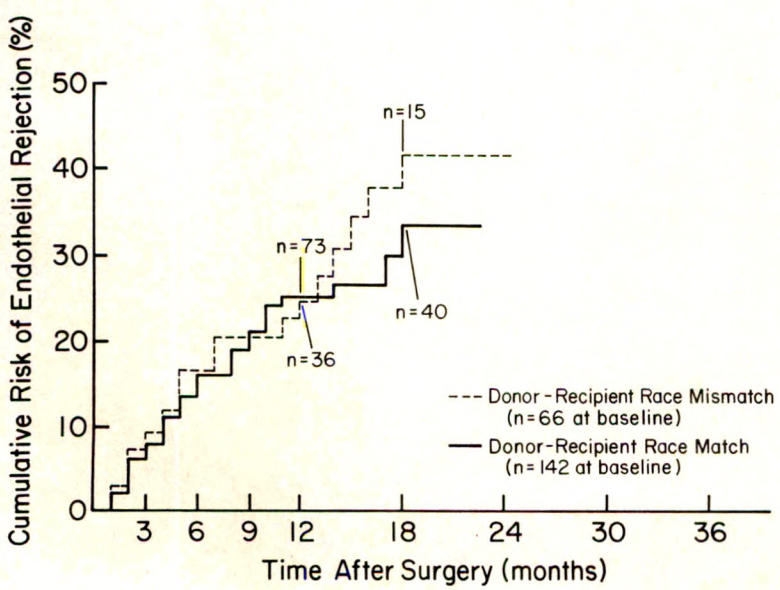


Fig. 2 (Musch and associates). Kaplan-Meier analysis of the risk of endothelial rejection after penetrating keratoplasty in race-matched and -mismatched, high-risk recipients (P = .40, Mantel-Cox test; P = .63, generalized Wilcoxon test).

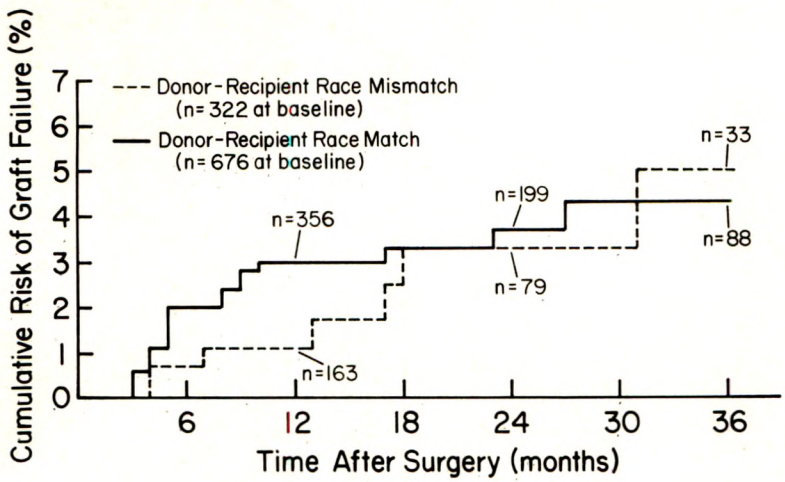


Fig. 3 (Musch and associates). Kaplan-Meier analysis of the risk of graft failure caused by endothelial rejection after penetrating keratoplasty in race-matched and -mismatched recipients (P = .54, Mantel-Cox test; P = .24, generalized Wilcoxon test).

lished investigations on the need for race matching in corneal transplantation, several studies in the renal transplantation literature have quantified actuarial graft survival rates by donor and recipient races, with inconsistent results.[7-11] No mismatch effect was found in several studies,[10,11] while a recent actuarial survival analysis of 889 cadaver renal transplant recipients reported that both graft and patient survivals are improved when donors and recipients are of the same race (black or white).[9] The degree to which results from renal transplantation studies can be related to corneal transplantation is probably small, however, because of the evident disparity in the two systems and procedures.

Given the random nature of corneal tissue distribution at our center, this retrospective outcome evaluation of corneal transplantation in race-matched and race-mismatched recipients can be considered a fortuitous randomized clinical trial. The two groups differ only on the comparability of the donor and recipient's race.

We found no significant difference in the cumulative risk of endothelial rejection and subsequent graft failure between race-matched and race-mismatched groups, both in the overall recipient population and in those at high risk of endothelial rejection before surgery. While our sample sizes were sufficiently large, so that adequate statistical power was available to detect meaningful differences in risk, long-term follow-up will be necessary to state with certainty that no difference will be seen at five or ten years after surgery. The long-term, post-keratoplasty natural progression of both outcomes (endothelial rejection and graft failure from an endothelial rejection) are not well enough delineated to permit us to conclude that no difference will be seen with further follow-up. Within the first two to three years after surgery, however, the race-matched and -mismatched groups did not show any statistical differences in the risk of each outcome.

Interestingly, the endothelial rejection survival curves of high-risk race-matched and -mismatched recipients show some suggestion of separation as follow-up continues, albeit lacking statistical difference. While only further follow-up will enable us to evaluate definitively this possible trend, it is in these recipients that HLA matching has been postulated to be effective in reducing the risk of endothelial rejection and graft failure,[14-16] and toward whom a multicenter clinical investigation is now directed.[17] Although an individual race mismatch does not necessarily imply a greater degree of HLA mismatch, the prevalence of HLA mismatches in the race-mismatched group is probably greater than that in the race-matched group, given the differences extant in the HLA-A and -B loci antigen frequencies for North American white and black populations.[18] Our lack of donor HLA typing information prevents us from quantifying the degree of HLA mismatch in our recipient group.

While we await the results of studies, such as the Collaborative Corneal Transplantation Studies,[17] to provide direction on the need for tissue matching in penetrating keratoplasty, this study provides no rationale for race matching of the corneal donor and the corneal transplant recipient in an effort to reduce the risk of endothelial rejection or graft failure caused by endothelial rejection.

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OPHTHALMIC MINIATURE

He suffered the strange pangs of a conscience suddenly operated on for a cataract. He could see what it revolted him to see.

Victor Hugo, *Les Miserables*
New York, New American Library, 1987, p. 1325

The Effect of Radial Keratotomy on Contrast Sensitivity

M. M. Krasnov, M.A.Sc., S. E. Avetisov, N. V. Makashova, and V. R. Mamikonian

In the period after surgical correction of myopia and astigmatism in 30 patients (44 eyes) by radial keratotomy, contrast sensitivity deteriorated slightly. The disturbances, however, were transitory, and the general trend was toward restoration of function. Strict adherence to an adequate operative technique prevented a marked decline in contrast sensitivity. The decrease must be considered before surgery, particularly in patients who need a high degree of fine motor control.

THE DEGREE OF reduction in myopia and astigmatism and postoperative corrected or uncorrected visual acuity are the primary criteria used to evaluate the effectiveness of surgical correction of myopia and astigmatism. Clinical experience has shown that after a technically adequate operation, both corrected and uncorrected visual acuity may be worse than before surgery. Some investigators emphasize that many patients complain of "visual discomfort," particularly during the first few postoperative months.

This phenomenon may be attributed to postoperative optical aberrations caused by distorted topographic relationships in the central part of the cornea, the development of irregular astigmatism, or opacities at the sites of the incisions that extend almost to the central optical zone. Measurements of maximum visual acuity with high-contrast optotypes do not reflect the influence of these aberrations on the resolution capacity of the eye. However, a more sensitive testing method, called contrast sensitivity, determines visual accuracy at medium contrast levels.[1]

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The purpose of this study was to evaluate the effect of surgical correction of myopia and astigmatism on contrast sensitivity.

Material and Methods

We studied 44 eyes of 30 patients. Eighteen eyes were myopic and 26 had myopic astigmatism. All eyes were examined preoperatively and then again at one to four weeks, 2½ to four months, and ten to 12 months after surgery. The reduction in myopia ranged from 3.5 to 7.5 diopters (mean, 5.75 diopters). The reduction in myopic astigmatism ranged from 1.0 to 3.75 diopters (mean, 2.85 diopters). Four to six radial corneal incisions were made in each eye, leaving an intact central zone that was 3 mm in diameter. A micrometer knife with a metal blade was used to create incisions 90% to 96% of the central thickness. Transpalpebral compression with a special meniscus was used postoperatively.[2]

Contrast sensitivity was studied on a television system. The size of the stimulation field corresponded to an angle of vision of 1.4 degrees at a distance of 5.0 m using a sinusoidal pattern. The spatial frequency of the patterns, that is, the number of cycles per degree of the visual angle, varied from 2 to 32. Contrast was changed discretely from 0.01 to 0.69 to produce 52 different levels. The threshold level was determined by increasing contrast from the subliminal level at a given spatial frequency until the patient could recognize the grid pattern. Thus, the threshold level for each pattern was the minimum contrast level required for resolution of the grid elements, which depended on the spatial frequency of the grid. The value reciprocal to the threshold level was designated contrast sensitivity.

Contrast perception was tested twice at each spatial frequency with the pattern oriented both vertically and horizontally. The two measurements were averaged to obtain the final result.

TABLE 1
PREOPERATIVE AND POSTOPERATIVE THRESHOLD LEVEL (MEAN ± S.D.)*

LENGTH OF FOLLOW-UP PERIOD	SPATIAL FREQUENCY (CYCLES/DEG)									
	VERTICAL PATTERNS					HORIZONTAL PATTERNS				
	2	4	8	16	32	2	4	8	16	32
Before surgery	0.0199	0.0122	0.0127	0.0431	0.5233	0.0207	0.0116	0.0153	0.0551	0.5285
	±0.0025	±0.0008	±0.0009	±0.0061	±0.0581	±0.0003	±0.0003	±0.0010	±0.0103	±0.0700
1 wk to 1 mo after surgery (n = 44)	0.0337	0.0209	0.0240	0.0768	0.6012	0.0437	0.0284	0.0357	0.1592	0.5954
	±0.0072	±0.0036	±0.0048	±0.0240	±0.0741	±0.0064	±0.0059	±0.0081	±0.0500	±0.0932
P value	NS	.05	.05	NS	NS	.01	.01	.05	.05	NS
Before surgery	0.0197	0.0153	0.0167	0.0630	0.4654	0.0247	0.0266	0.0396	0.0884	0.5107
	±0.0020	±0.0015	±0.0018	±0.0018	±0.0555	±0.0045	±0.0082	±0.0230	±0.0339	±0.0426
2.5 to 4 mos after surgery (n = 40)	0.0353	0.0240	0.0282	0.1029	0.5059	0.0741	0.0414	0.0363	0.1372	0.6126
	±0.0048	±0.0029	±0.0043	±0.0203	±0.0786	±0.0253	±0.0074	±0.0074	±0.0446	±0.0467
P value	.01	.01	.05	NS	NS	NS	NS	NS	NS	NS
Before surgery	0.0190	0.0153	0.0166	0.0952	0.4955	0.0284	0.0182	0.0260	0.0587	0.5159
	±0.0022	±0.0020	±0.0015	±0.0515	±0.0653	±0.0064	±0.0048	±0.0548	±0.0183	±0.0890
10 to 12 mos after surgery (n = 36)	0.0177	0.0134	0.0169	0.0625	0.4920	0.0343	0.0280	0.0247	0.1094	0.5072
	±0.0013	±0.0019	±0.0033	±0.0176	±0.0744	±0.0084	±0.0084	±0.0073	±0.0325	±0.0712
P value	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

*NS, not significant.

Results

The results of assessing the contrast sensitivity curve at different intervals after the operation are presented in Table 1 and Figures 1 through 3. The mean values of maximum visual acuity were similar before and after surgery (Table 2). At up to four months after surgery, there was a slight reduction in maximum visual acuity. At the same time there was a decline in contrast sensitivity, as indicated by higher threshold level values at all levels of spatial frequency. However, while the difference between preoperative and postoperative mean threshold level values within the first month after surgery was significant at six of ten spatial frequency levels, it retained statistical significance at only three spatial frequency levels by the end of four months. This demonstrated the general trend of restoration of normal contrast sensitivity. Subsequently, this difference became nonsignificant at all spatial frequency levels. Thus, the early tendency of an increase in threshold level disappeared. Moreover, there was an increase in contrast sensitivity. At six of ten spatial frequency levels (2, 4, 16, and 32 cycles per degree for vertical, and 8 and 32 cycles per degree for horizontal patterns), postoperative mean threshold level values were lower than before the operation, while contrast sensitivity was correspondingly higher.

TABLE 2
PREOPERATIVE AND POSTOPERATIVE VISUAL ACUITY

LENGTH OF FOLLOW-UP PERIOD*	VISUAL ACUITY (MEAN ± S.D.)	
	PREOPERATIVE	POSTOPERATIVE
1 wk to 1 mo (n = 44)	0.91 ± 0.0259	0.88 ± 0.0225
2.5 to 4 mos (n = 40)	0.90 ± 0.0112	0.86 ± 0.0148
10 to 12 mos (n = 36)	0.83 ± 0.0239	0.83 ± 0.0258

*Some eyes were lost to follow-up over time.

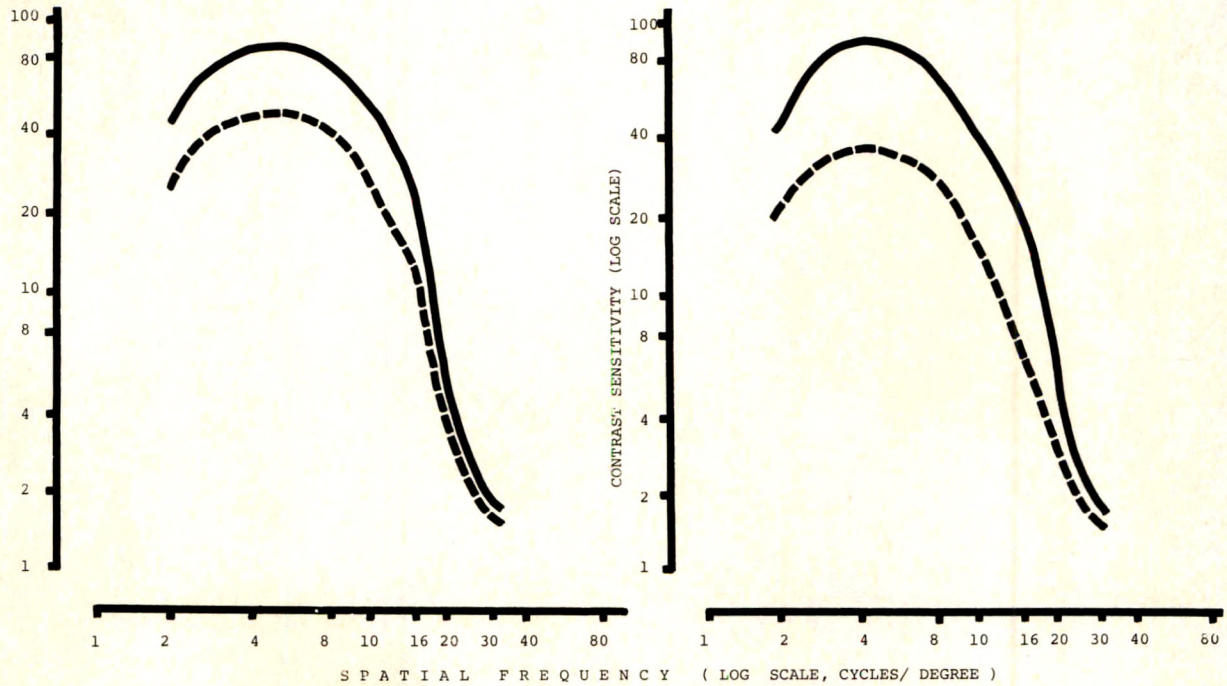


Fig. 1 (Krasnov and associates). The contrast sensitivity curves before (solid lines) and one week to one month after (dotted lines) surgery. A, vertical patterns; B, horizontal patterns.

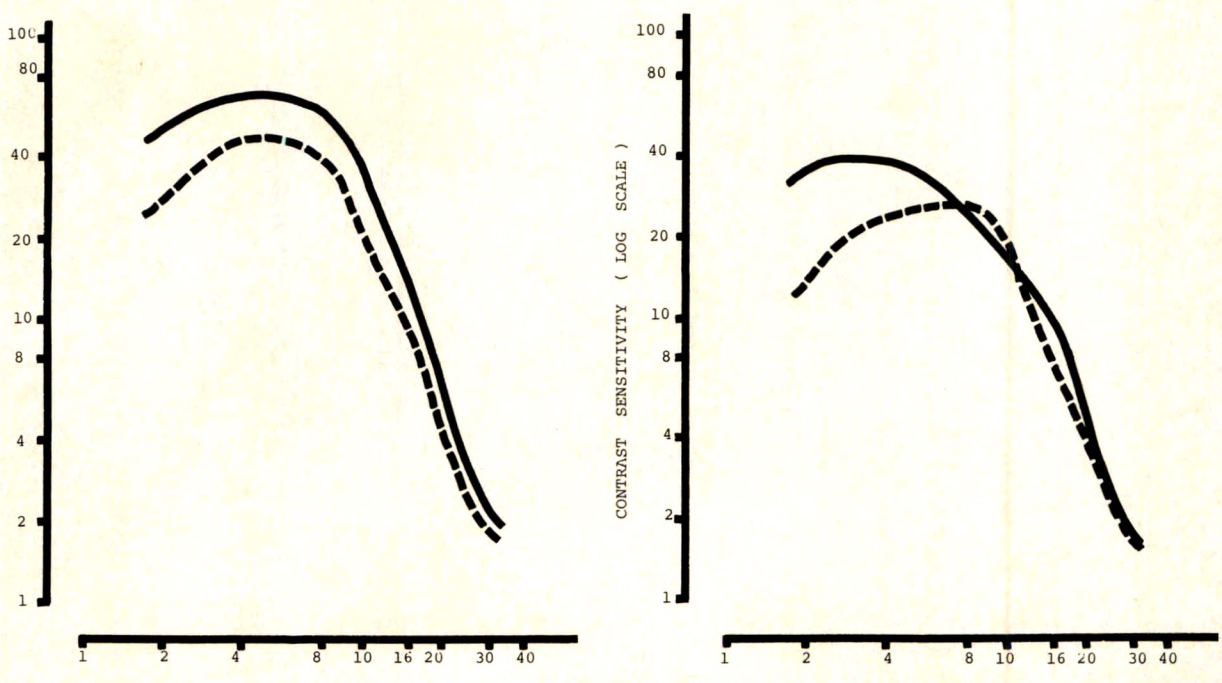


Fig. 2 (Krasnov and associates). The contrast sensitivity curves before (solid lines) and 2.5 to four months after (dotted lines) surgery. A, vertical patterns; B, horizontal patterns.

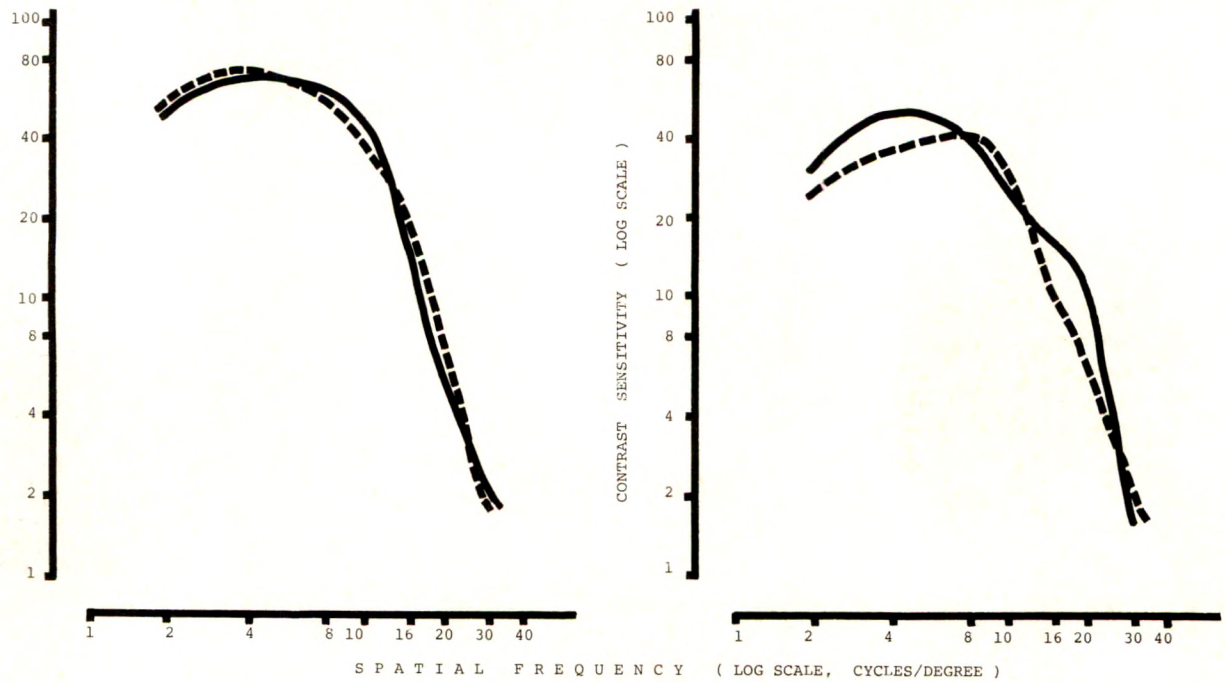


Fig. 3 (Krasnov and associates). The contrast sensitivity curves before (solid lines) and ten to 12 months after (dotted lines) surgery. A, vertical patterns; B, horizontal patterns.

Discussion

Deterioration of contrast sensitivity in the early postoperative period is caused by aberrations from irregular astigmatism (keratometry shows distortion of mires and loss of mutually perpendicular arrangement of principal meridians). Another cause is density of the termination of corneal incisions in the optical zone, which may result in diffraction. Irregular astigmatism does not usually persist in the following months, and corneal opacities of the cornea become less dense. This leads to restoration of contrast sensitivity ten to 12 months after the operation.

Thus, it is necessary to ensure a proper configuration of the intact central zone and to make the incisions carefully to prevent the formation of coarse postoperative scars.

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Necrotizing Keratitis Caused by *Capnocytophaga ochracea*

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We studied three cases of *Capnocytophaga* keratitis that demonstrated stromal necrosis and a ring infiltrate. In all cases, the keratitis occurred in a previously diseased or traumatized cornea. One patient was treated with chronic antiamoebic therapy for presumed *Acanthamoeba* keratitis. Two cases resulted in corneal perforation. Laboratory isolation was difficult because of slow, fastidious growth. *Capnocytophaga* is not uniformly sensitive to commonly used topical antibiotics such as the cephalosporins and aminoglycosides, but may respond to treatment with topical clindamycin.

CAPNOCYTOPHAGA (formerly *Bacteroides ochracea* and Centers for Disease Control biogroup DF-1) is a gram-negative fusiform-shaped bacterium, known for its gliding motility and capnophilic (CO_2-loving) metabolism.[1-3] *Capnocytophaga* is part of the normal human oral flora and is sometimes found in sputum and throat specimens. It is a frequent cause of periodontitis and has caused a variety of infections in immunocompromised and neutropenic patients.[4-9] Recently, *Capnocytophaga* has been found to cause infections in nonimmunocompromised patients.[10] *Capnocytophaga* conjunctivitis and canaliculitis have been reported.[10,11] To our knowledge, only two cases of *Capnocytophaga* keratitis have been reported, both occurring in previously diseased or traumatized corneas.[12] We report three additional cases that emphasize the clinical features of stromal ring infiltrate associated with a necrotizing keratitis, endothelial plaque, and potential for severe inflammatory response. This organism must be considered in cases of necrotizing keratitis, since laboratory isolation may be difficult and it is relatively resistant to conventional topical antimicrobial therapy.

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Case Reports

Case 1

A 30-year-old woman was struck in the right eye with a piece of paper in December 1986 and developed a corneal abrasion, which healed in two days with pressure patching. In March 1987 she noted recurrent pain and redness in her right eye and was treated with a three-week course of unknown topical antibiotics for ulcerative keratitis with no improvement. She was referred to the Bascom Palmer Eye Institute on April 8, 1987. Visual acuity in the right eye was hand motions. Slit-lamp examination demonstrated a central epithelial defect with a ring stromal infiltrate (Fig. 1). A presumptive clinical diagnosis of *Acanthamoeba* keratitis was made, and a corneal scraping and biopsy were performed. Gram, Giemsa, and calcofluor white stains were negative, and there was no growth on *Escherichia coli* overlaid nonnutrient blood agar. She was treated with topical 0.1% propamidine isethionate every hour, topical homatropine, paromomycin, 1% prednisolone phosphate, and clotrimazole cream four times a day, and 200 mg of ketoconazole by mouth daily. Eight days later, a second corneal biopsy was performed, but Gram, Giemsa, and calcofluor white stains as well as cultures on *E. coli* overlaid nonnutrient blood agar were negative for *Acanthamoeba*.

The keratitis worsened, and a severe anterior chamber reaction developed. Cyanoacrylate tissue adhesive was placed on the temporal biopsy site on May 25, 1987, because of impending perforation. On June 8, 1987, a massive necrotizing keratitis associated with a corneal perforation at the inferior biopsy site was

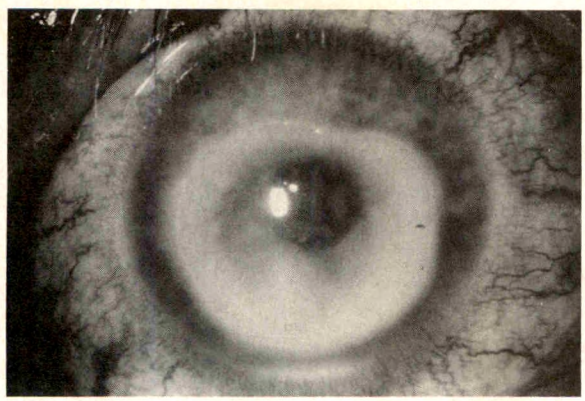


Fig. 1 (Heidemann and associates). Case 1. Central epithelial defect with double ring stromal infiltrate.

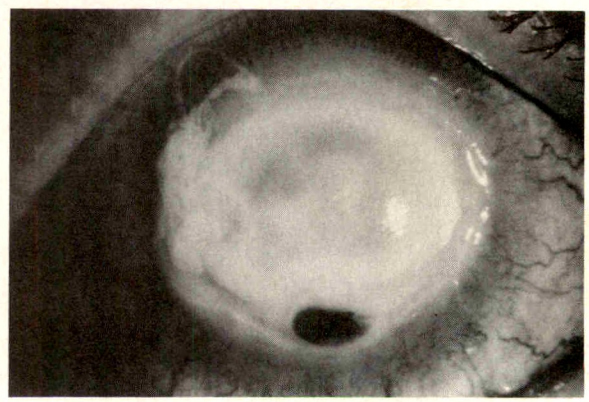


Fig. 2 (Heidemann and associates). Case 1. Necrotizing keratitis with corneal perforation at inferior biopsy site.

noted (Fig. 2). A 12-mm penetrating keratoplasty with stripping of inflammatory membranes was performed on the same day. Histopathologic examination showed massive polymorphonuclear cell infiltration and necrosis, but no *Acanthamoeba* cysts, trophozoites, or other organisms. Postoperative treatment consisted of hourly topical fortified cefazolin (50 mg/ml) and Neosporin, as well as oral ketoconazole (200 mg/day) and prednisone (60 mg/day). On June 12, 1987, *C. ochracea* was cultured from the corneal button on four different media, including blood and chocolate agar under increased carbon dioxide tension, blood agar in an anaerobic jar, and thioglycolate broth. A persistent epithelial defect was present postoperatively, and on July 1, 1987, a superior peripheral stromal ring infiltrate was noted. Corneal scrapings were performed and yielded no growth. The infiltrate and anterior chamber reaction increased, and on July 10, 1987, oral azathioprine (50 mg/day) was prescribed for presumed allograft rejection. The clinical course worsened, and on July 15, 1987, a repeat 12-mm penetrating keratoplasty was performed. Postoperatively, the corneal epithelium did not heal and a tarsorrhaphy was performed. It was subsequently discovered that she had been frequently and regularly using topical tetracaine and proparacaine since her symptoms began in March 1987. All topical medications were stopped, and the epithelium healed within several weeks. Visual acuity in December 1987 was light perception with projection. The graft was edematous and an intumescent cataract was present.

Case 2

A 40-year-old man was splashed in his left eye with an organic solvent used for stripping paint on June 22, 1986. His eyes were immediately irrigated with water and he was referred to the Bascom Palmer Eye Institute. Visual acuity was 20/400 in the left eye, with moderate conjunctival injection and a large central epithelial defect. There was a mild anterior chamber reaction. Treatment consisted of pressure patching, bacitracin zinc-polymyxin B sulfate ointment, and 5% homatropine eyedrops two times daily. After initial improvement, a total epithelial defect developed with diffuse stromal edema, Descemet's folds, and moderate anterior chamber reaction. Treatment was changed to topical tobramycin (3 mg/ml), 1% prednisolone acetate, and 1% cyclopentolate four times daily. The epithelium began to heal, but on July 1, 1986, a peripheral stromal ring infiltrate with a large central endothelial plaque developed. The patient was treated with 80 mg of prednisone by mouth daily. Results of B-scan ultrasonography of the posterior segment were normal. On July 9, 1986, the anterior chamber reaction increased and a 60% hypopyon was present (Fig. 3). Corneal scrapings were performed for smears and cultures. Gram and Giemsa stains demonstrated inflammatory cells but no organisms. On July 11, 1986, a corneal biopsy and anterior chamber lavage were performed. Peripheral corneal thinning developed and cyanoacrylate tissue adhesive was placed because of peripheral corneal thinning and impending perforation. By July 15, 1986, cultures of both the corneal scraping and biopsy yielded

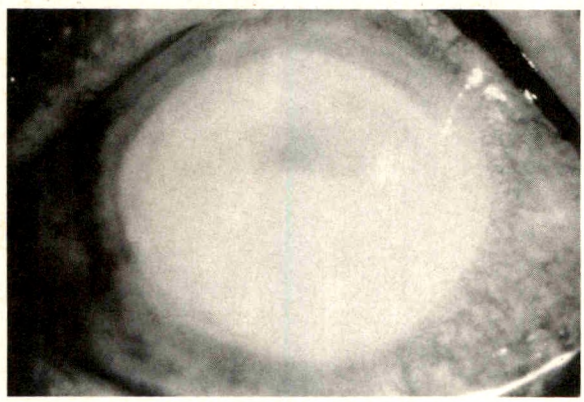


Fig. 3 (Heidemann and associates). Case 2. Ring infiltrate, endothelial plaque, and 60% hypopyon.

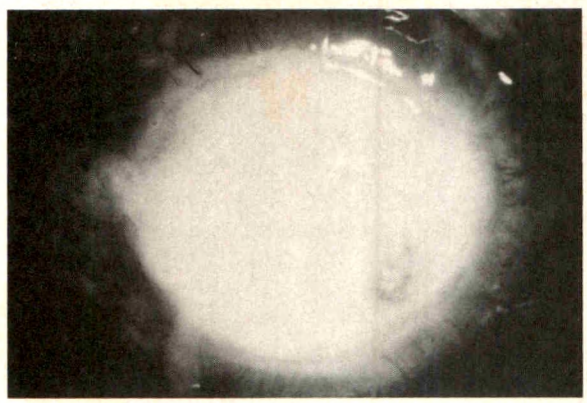


Fig. 4 (Heidemann and associates). Case 2. Massive stromal necrosis and corneal perforation.

growth of *C. ochracea* on blood agar in the anaerobic jar, sensitive to clindamycin and penicillin. Treatment was initiated with topical fortified penicillin (100,000 units/ml) and clindamycin (50 mg/ml) every 30 minutes. On July 19, 1986, cyanoacrylate tissue adhesive was applied to the superior peripheral cornea because of impending perforation. On July 25, 1986, diffuse stromal necrosis and a central corneal perforation plugged with necrotic debris was noted (Fig. 4). On the same day, a 12-mm penetrating keratoplasty, anterior chamber membranectomy, synechialysis, and iridectomy were performed. Histopathologic examination showed diffuse polymorphonuclear cell infiltration and necrosis, but no organisms. Cultures of the corneal button were negative. The postoperative course was marked by an intense anterior chamber inflammatory reaction. On Oct. 19, 1986, an edematous cornea and flat anterior chamber secondary to an intumescent lens were noted. The next day, a lens aspiration, anterior chamber membranectomy, and synechialysis were performed. Three months postoperatively, the patient had diffuse corneal edema, normal intraocular pressure, and a visual acuity of light perception.

Case 3

An 83-year-old woman with a 20-year history of open-angle glaucoma had bilateral band keratopathy and a visual acuity of hand motions in the right eye. On Aug. 20, 1987, she underwent a superficial keratectomy in the right eye. She was treated with topical tobramycin (3 mg/ml) and 1% prednisolone acetate four times daily, 250 mg of oral tetracycline four times daily, and pressure patching. On Sept. 22, 1987, a bandage contact lens was placed because of a nonhealing epithelial defect. Six days later, slit-lamp examination disclosed a large central epithelial defect, with a partial stromal ring infiltrate, and an area of stromal necrosis, with approximately 25% thinning (Fig. 5). Visualization of the anterior chamber was difficult. Corneal scrapings were performed, and treatment with hourly topical cefazolin (50 mg/ml) and tobramycin (14 mg/ml) was initiated. Three days later, cultures of both cornea and contact lens yielded growth of a gram-negative rod on chocolate and blood agar incubated under increased carbon dioxide tension. The organism was sensitive to cefazolin, but resistant to to-

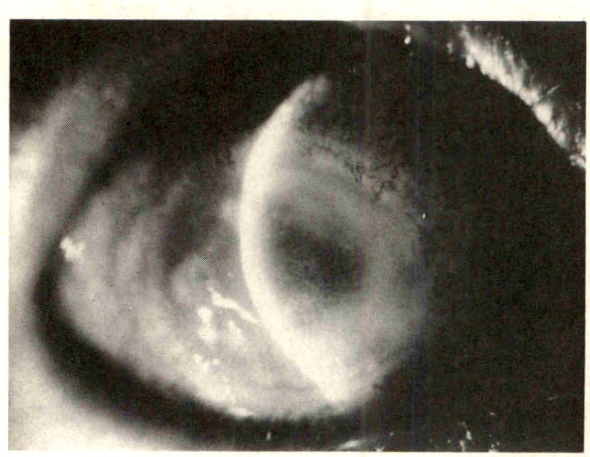


Fig. 5 (Heidemann and associates). Case 3. Central epithelial defect with stromal necrosis and partial ring infiltrate.

bramycin and gentamicin. The organism was later identified as *C. ochracea* by the Michigan Department of Public Health. The patient responded slowly to treatment with topical cefazolin (50 mg/ml). On Oct. 28, 1987, visual acuity was light perception and slit-lamp examination showed one pinpoint area of fluorescein stain, resolution of the infiltrate, superficial vascularization, and minimal anterior chamber reaction.

Discussion

Capnocytophaga is a dysgonic fermenter, and produces a yellow pigment on solid media. DNA base homology, biochemistry, and morphologic studies have yielded three species: *C. ochracea*, *C. sputigena*, and *C. gingivalis*.[13-16]

Capnocytophaga ochracea was formerly known as *Fusobacterium nucleatum* var. *ochraceus*, *Ristella ochracea*, and *Bacteroides oralis* var. *elongatus*.[2] It was later identified as *Bacteroides ochraceus* or Centers for Disease Control biogroup DF-1. The taxonomy was rather confusing until recently, when two independent reports established that *B. ochracea*, Centers for Disease Control biogroup DF-1, and *Capnocytophaga* were synonymous.[1,2]

The two previously described patients with *Capnocytophaga* keratitis exhibited similar clinical features to our three patients (Table).[12] These two cases plus our three cases all occurred in previously diseased or traumatized corneas. In our three cases, each patient was receiving topical corticosteroids. Patient 1 was also receiving topical anesthetics and chronic antiamoebic therapy, which may have further predisposed her to infection. Secondary bacterial infectious keratitis developing during the treatment of *Acanthamoeba* keratitis has previously been reported.[17-19]

In the five total cases, four patients had a peripheral stromal ring infiltrate, four patients had an inflammatory endothelial plaque, and two patients developed a severe anterior chamber inflammatory reaction and corneal perforation. *Capnocytophaga* produces various pathogenic factors leading to complex interactions with host defenses. *Capnocytophaga ochracea* produces a protease that can degrade IgA-1 and polyclonal IgG, which may decrease local defenses and contribute to pathogenicity.[20] *Capnocytophaga ochracea* produces a heat-stable, dialyzable substance that alters local neutrophil migration and morphology,[21] but it did not prevent massive neutrophil infiltration in our Patients 1 and 2. This neutrophil infiltration may have been caused by endotoxin-mediated alternate pathway complement fixation. All three species of *Capnocytophaga* produce an endotoxin.[20] Many *Capnocytophaga* infections occur in patients who are neutropenic or have hematologic malignancies.[4-10,21] Patient 1 had a persistently increased white blood cell count of greater than 20,000/mm^3, but refused to undergo a bone marrow biopsy.

Clinically, a necrotizing keratitis with stromal ring infiltrate may suggest several diagnos-

TABLE
CLINICAL FEATURES OF *CAPNOCYTOPHAGA* KERATITIS

INVESTIGATORS	AGE (YRS), SEX	HISTORY	DIAGNOSTIC METHOD	STROMAL RING INFILTRATE AND NECROSIS	TOPICAL TREATMENT AND OUTCOME
Roussel, Osato, and Wilhelmus	43, F	Corneal edema	Corneal scraping	No	Clindamycin; healed
Roussel, Osato, and Wilhelmus	35, M	Blunt trauma	Corneal scraping	Yes	Clindamycin; healed
Present study					
Case 1	30, F	Anesthetic abuse	Corneal button	Yes	Propamidine, clotrimazole, paromomycin; perforation; penetrating keratoplasty ×2; failed
Case 2	40, M	Chemical injury	Corneal scraping and biopsy	Yes	Penicillin, clindamycin; perforation; penetrating keratoplasty; failed
Case 3	83, F	Epithelial debridement	Corneal scraping and contact lens	Yes	Cefazolin, tobramycin; healed

tic possibilities, including *Acanthamoeba*, herpes simplex, anesthetic abuse, as well as *Pseudomonas*, *Proteus*, or other endotoxin-producing gram-negative bacteria. In our three patients, the infiltrate was initially dry and did not have the typical appearance of suppurative keratitis caused by a gram-negative organism such as *Pseudomonas*. All three patients, however, later developed massive necrotizing keratitis. The history of a previously diseased or compromised cornea, the clinical appearance, and the slow, insidious onset with relentless progression may be especially suggestive of *Acanthamoeba* keratitis. Patient 1 was treated for presumed *Acanthamoeba* keratitis, but culture and stain of two corneal biopsy specimens and the corneal button did not confirm this diagnosis. The ring infiltrate may have been caused by chronic anesthetic abuse and it is not known if *Capnocytophaga* caused a primary or secondary infection.

Isolation of *Capnocytophaga* is difficult and the diagnosis may be missed if proper culture technique is not used. *Capnocytophaga* is a facultative anaerobe and requires a CO_2-enriched atmosphere for growth. It may grow on CO_2-enriched blood or chocolate agar or may grow only on anaerobic media.[5] In Case 1, results of early corneal scrapings and biopsy specimens were negative, but were performed while the patient was receiving topical antibiotics. Later, cultures of the corneal button grew *Capnocytophaga* on CO_2-enriched blood and chocolate agar, blood agar in the anaerobic jar, and thioglycolate broth. In Case 2, cultures of the corneal scrapings and biopsy specimen grew *Capnocytophaga* in anaerobic media only. In Case 3, cultures of corneal scrapings and the contact lens grew *Capnocytophaga* on CO_2-enriched blood and chocolate agar. In all three cases, growth was not noted until three or more days after inoculation. *Capnocytophaga* is a fastidious organism, and even when proper culture media and technique are used, isolation may be difficult because of slow growth or overgrowth by other organisms in uncommon instances of mixed infections or contaminated specimens.[1] This emphasizes the importance of routinely stopping antibiotics before cultures, using media incubated in increased carbon dioxide tension and anaerobic conditions, and holding cultures for greater than three days when evaluating infectious keratitis. If cultures are negative and the clinical course worsens, corneal biopsy should be considered.

Capnocytophaga is sensitive to antimicrobial agents that have the greatest activity against anaerobes. In vitro sensitivity testing of *Capnocytophaga* has demonstrated sensitivity to clindamycin, penicillin, chloramphenicol, tetracycline, and carbenicillin, with relative resistance to aminoglycosides, polymyxins, and vancomycin. Sensitivity to the cephalosporins is variable.[22,23] Recently, beta-lactamase-producing strains have been reported.[24] Both patients described by Roussel, Osato, and Wilhelmus[12] did not respond to initial therapy with topical and subconjunctival cefazolin or gentamicin, but healed with topical and subconjunctival clindamycin. Of our cases, one patient (Patient 3) healed slowly with topical cefazolin. The other two patients developed a severe necrotizing keratitis, resulting in corneal perforation. One patient (Patient 2) did not respond to appropriate topical therapy with penicillin and clindamycin, but the diagnosis was made late in the clinical course. The cornea of the other patient (Patient 1) perforated while the patient was receiving long-term antiamoebic therapy. Based on these cases as well as in vitro sensitivity testing, topical clindamycin may be the most effective treatment for *Capnocytophaga* keratitis.

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OPHTHALMIC MINIATURE

It is only a vision of what is Not Possible, for there is only reality, and man is reality, and what is seen and felt and smelled and tasted and heard with our senses is the only objectivity, and only truth. We are too Advanced for myths; we have achieved maturity and wisdom and intellect. Begone with Myths!

Taylor Caldwell, *Dialogues With The Devil*
New York, Fawcett World Library, 1967, p. 14

Mycobacterium fortuitum Keratitis

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Two of four cases of *Mycobacterium fortuitum* keratitis occurred after corneal surgery with contact lens wear, one was associated with extended contact lens wear alone, and one occurred after a foreign body injury. All cases were characterized by pain, conjunctival hyperemia, stromal inflammation, and ulceration. Diagnosis was made by culture and acid-fast staining of corneal scrapings. On the basis of published experience with amikacin for the treatment of nonocular *M. fortuitum* infections, three patients were treated with topical amikacin. Two patients responded clinically, but histopathologic examination of a penetrating keratoplasty specimen in one of the two disclosed persistent infection. One patient was cured of early disease by debridement alone. Rapid diagnosis and absence of corticosteroid use were the two most important determinants of successful therapy. In advanced cases, infection may be cured and useful vision restored by penetrating keratoplasty.

A NONTUBERCULOUS MYCOBACTERIUM, *Mycobacterium fortuitum* is widespread in the environment.[1] Long considered nonpathogenic, the atypical mycobacteria, including *M. fortuitum*, are now known to be capable of causing severe opportunistic human infections,[2,3] including indolent keratitis. Since the first report by Turner and Stinson in 1965,[4] a total of 12 cases of *M. fortuitum* keratitis have been reported.[5-11] Most cases have occurred after foreign body injury to the cornea. The keratitis has been characterized by an indolent course and resistance to antibiotics including conventional antituberculosis drugs. Visual outcome usually has been poor.

Described herein are four additional cases. In only one did infection occur after foreign body injury; the remaining infections were associated with surgery and contact lens use. On the basis of published experience with amikacin for the treatment of related infections,[12] topical amikacin was used to treat the keratitis in three patients.

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Case Reports

Case 1

A 35-year-old woman with severe myopia who had worn hard contact lenses for 15 years without problems developed pain in both eyes after receiving new lenses. A corneal abrasion occurred in the left eye four months later without ocular trauma or toxic exposure. The epithelial defect healed with pressure patching, but pain persisted. Prednisolone acetate 1% was administered four times daily without relief of symptoms, and a two-week trial of an extended-wear soft contact lens did not help.

Examination disclosed a corrected visual acuity of R.E.: 20/25 and L.E.: 20/50. The right cornea was normal. The left cornea had a round 1-mm diameter epithelial defect with irregular surrounding epithelium located 2 mm from the 12 o'clock meridian of corneoscleral limbus. It did not heal with pressure patching for 48 hours. There were no stromal infiltrates; nor was there anterior chamber reaction. Pain increased, the epithelial defect enlarged, and a diffuse multifocal epithelial keratopathy, characterized by discrete areas of epithelial opacification with central defects, developed. A trial of trifluridine 1% nine times daily was given for a possible herpes simplex virus infection. After four days the epithelial defect healed and the multifocal keratopathy resolved. The epithelium in the area of the healed defect continued to

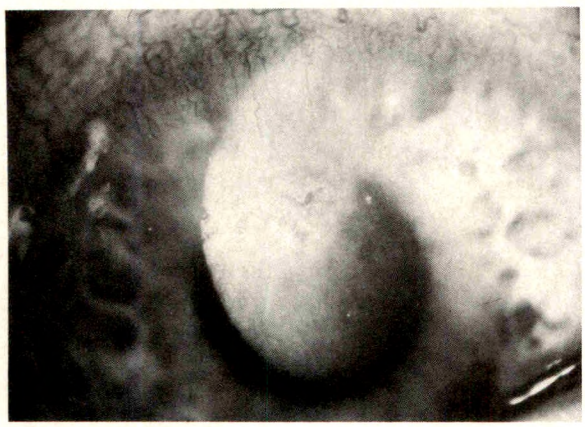


Fig. 1 (Dugel and associates). Case 1. Focal epithelial keratopathy in the left eye one month after development of contact lens-associated epithelial defect.

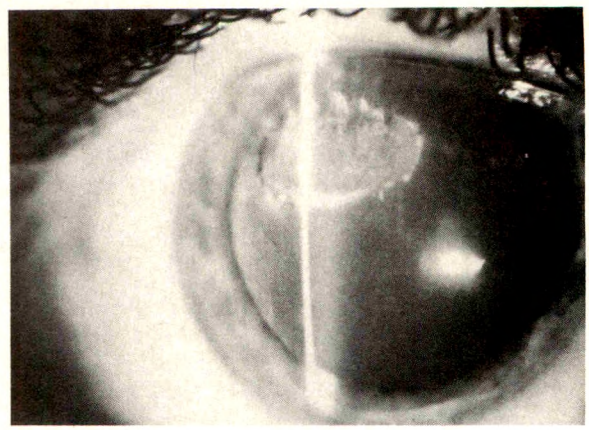


Fig. 2 (Dugel and associates). Case 1. Stromal infiltration has developed at inferior border of persistent epithelial defect after initiation of topical corticosteroid therapy.

be irregular, tiny keratic precipitates developed, and occasional anterior chamber cells were seen. Trifluridine therapy was discontinued. Over the next two weeks, stromal infiltrates and edema developed under the irregular epithelium, and the epithelial defect recurred. Superficial corneal neovascularization extended from the superior corneoscleral limbus toward the lesion (Fig. 1). Epithelial debridement was performed and trifluridine therapy was restarted. Viral culture was negative. The epithelial defect and stromal infiltrates persisted, and pain increased over the next ten days.

Prednisolone acetate 1% was given four times daily and pain subsided. Two weeks later a deep stromal infiltrate developed at the inferior margin of the epithelial defect (Fig. 2). There was no improvement with topical fortified cefazolin and tobramycin. A corneal biopsy specimen was cultured and *M. fortuitum* grew on Lowenstein-Jensen media after three days. Therapy with topical fortified amikacin (50 mg/ml hourly) and oral doxycycline (100 mg twice daily) was begun, but the cornea thinned rapidly (Fig. 3). An 8-mm penetrating keratoplasty was performed one week later. Sensitivity testing later showed in vitro resistance to rifampin, streptomycin, ethambutol, isoniazid, para-aminosalicylic acid, cefoxitin, doxycycline, and amikacin.

Histologic sections of the thinned cornea disclosed a superficial ulcer extending into the anterior stroma. The remaining stroma was diffusely infiltrated by acute inflammatory cells. Within the midstroma focal aggregates of macrophages and cellular debris were present. Similar collections of macrophages were adherent to the endothelium (Fig. 4). Numerous slender, beaded, acid-fast rods were present within mononuclear cells and in the extracellular tissue of the stroma (Fig. 5). No organisms were found in the keratic precipitates.

Eight months after surgery the patient was symptom-free with no recurrence of corneal infiltration. Visual acuity was L.E.: 20/30.

Case 2

A 44-year-old woman with no history of surgery or ocular trauma reported loss of vision in the right eye. Corrected visual acuity was R.E.:

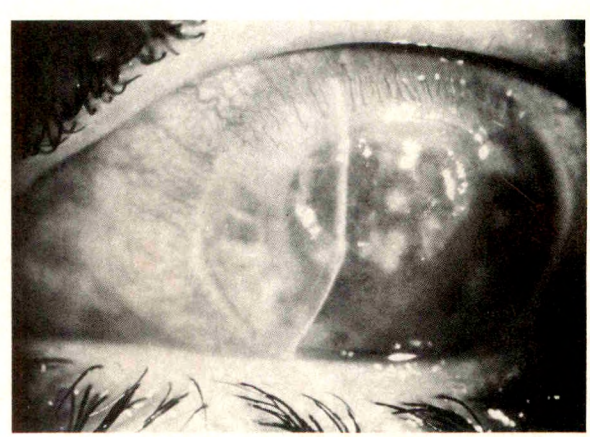


Fig. 3 (Dugel and associates). Case 1. Preoperative appearance of *M. fortuitum* keratitis showing multiple stromal infiltrates.

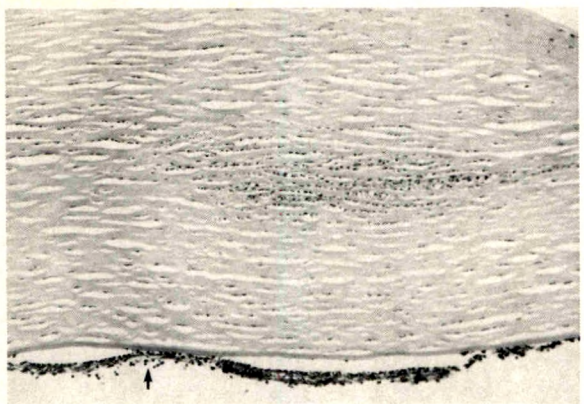


Fig. 4 (Dugel and associates). Case 1. A diffuse acute inflammatory stromal infiltrate with a focal aggregate of macrophages and cellular debris is present. Macrophages are adherent to the endothelium (arrow) (hematoxylin and eosin, ×100).

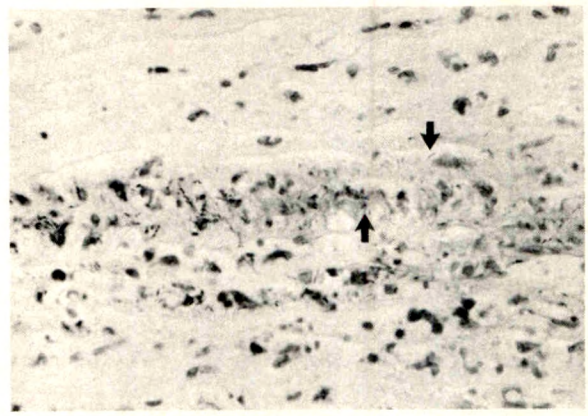


Fig. 5 (Dugel and associates). Case 1. Numerous acid-fast bacilli are found both intracellularly and extracellularly within inflammatory cell aggregates (arrows) (modified Ziehl-Neelson, ×630).

light perception and L.E.: 20/20. A central corneal scar of unknown cause and a dense cataract were present in the right eye. Penetrating keratoplasty and cataract extraction were performed and an extended-wear soft contact lens was placed. The patient did not return for examinations until one month later when graft failure and corneal vascularization were found. No improvement occurred with a treatment regimen of topical dexamethasone, atropine, trifluridine, gentamicin, and tobramycin.

Sixteen months later visual acuity was R.E.: light perception and L.E.: 20/20. Many irregularly shaped white stromal infiltrates were present in the graft (Fig. 6). Keratic precipitates and anterior chamber cells were present. Culture of corneal scrapings on Lowenstein-Jensen media grew *M. fortuitum*. Topical amikacin (100 mg/ml hourly) and oral doxycycline (100 mg twice daily) therapy was administered. The organisms later were found to be resistant to streptomycin, isoniazid, ethambutol, para-aminosalicylic acid, rifampin, gentamicin, tobramycin, and amikacin.

Repeat penetrating keratoplasty was performed. Examination of the failed graft showed dense focal collections of acid-fast bacilli within keratocytes and stromal macrophages and extracellularly between corneal lamellae. Minimal chronic inflammatory cells also were present (Figs. 7 and 8). In a rim of host tissue removed with the failed graft there was dense perivascular infiltration of lymphocytes in the stroma and numerous acid-fast bacilli (Fig. 9). Cytolog-



Fig. 6 (Dugel and associates). Case 2. *Mycobacterium fortuitum* keratitis in failed corneal graft of the right eye. Multiple stromal infiltrates are similar in appearance to those in Case 1 (Fig. 3).

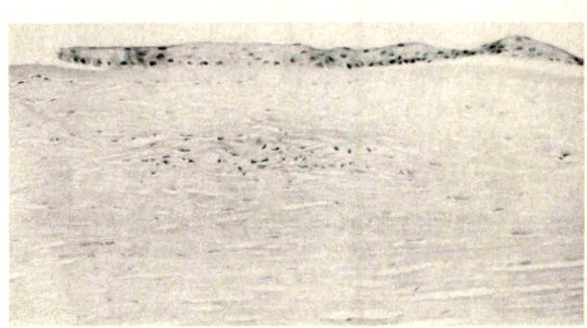


Fig. 7 (Dugel and associates). Case 2. A collection of mononuclear cells and granular material is present without stromal necrosis (hematoxylin and eosin, ×100).

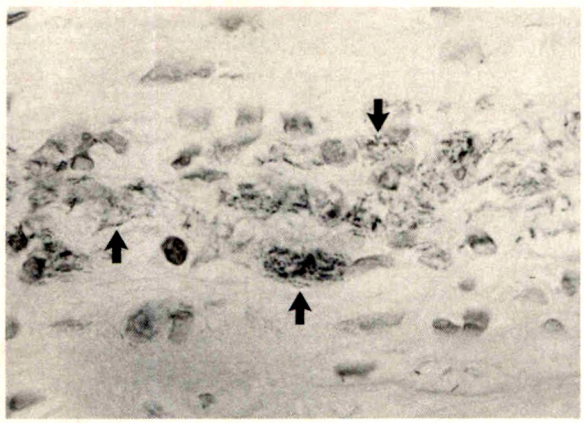


Fig. 8 (Dugel and associates). Case 2. Innumerable microorganisms are present, many of which appear to be extracellular (arrows) (modified Ziehl-Neelson, ×630).

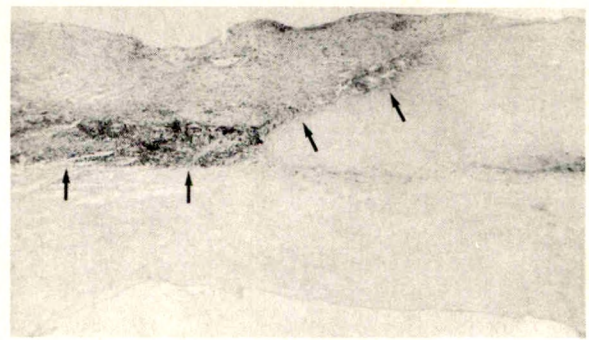


Fig. 9 (Dugel and associates). Case 2. A marked perivascular lymphocytic infiltrate is present within the host stroma at the donor-host interface (arrows) (hematoxylin and eosin, ×25).

ic preparation of vitreous removed during surgery contained abundant chronic inflammatory cells and acid-fast bacilli within macrophages and as extracellular aggregates.

Graft failure occurred three weeks postoperatively. No organisms grew from corneal scrapings placed on Lowenstein-Jensen media. A third penetrating keratoplasty was performed. The failed graft disclosed stromal scarring and marked endothelial attenuation. A few acid-fast organisms were found focally in the deep stroma adjacent to the wound margin (Fig. 10). Although no inflammatory reaction was seen in the stroma, a few lymphocytes were noted in a retrocorneal fibrous membrane.

Five months after surgery the third graft was clear without evidence of recurrent infection in the host or donor tissue. Vision was reduced to light perception by an inoperable retinal detachment.

Case 3

An 80-year-old man had a penetrating keratoplasty and anterior vitrectomy for aphakic corneal edema in the right eye. Visual acuity improved to 20/25 with an aphakic contact lens. Topical corticosteroids were used and occasionally the contact lens was left on the eye overnight. A large dendriform epithelial lesion developed on the graft 20 months after surgery. Topical corticosteroid use was discontinued and vidarabine ointment was given five times daily for presumed herpes simplex virus keratitis. The lesion did not resolve. Eight weeks later visual acuity was counting fingers at 3 feet. The entire graft was edematous and there was superior superficial vascularization. A 2-mm corneal ulcer surrounded by 1 to 2 mm of infiltrate extended into the midstroma nasal to the visual axis. There was a 3+ cellular reaction in the anterior chamber without hypopyon.

Corneal scrapings disclosed a few pleomorphic gram-negative bacilli, moderate gram-positive cocci, and many acid-fast bacilli. *Mycobacterium fortuitum* grew on Lowenstein-Jensen media after three days and was sensitive to amikacin on in vitro testing. Amikacin therapy was begun: one drop of a 100-mg/ml solution three to five times an hour and a subconjunctival injection of 20 mg/0.5 ml each day. There was no further stromal necrosis and re-epithelialization began within five days. Subconjunctival injections were discontinued on the 14th day and topical therapy was changed to amikacin 25 mg/ml, one drop every four hours while the patient was awake. Subepithelial and stromal vascularization developed, but the epithelium remained intact and there was no evidence of active disease five weeks later. Repeat studies for acid-fast bacilli were negative. Visual acuity remained counting fingers at 6 inches.

Case 4

A 26-year-old man, who was an auto mechanic, complained of a painful red left eye after drilling on metal. Two days later a small rusted corneal foreign body at the 3 o'clock meridian of the pupillary margin was removed. Prednisolone acetate-neomycin ointment was applied and the eye was patched. Two weeks later the patient complained of increasing pain. An epithelial defect persisted despite patching, curettage, and cauterization.

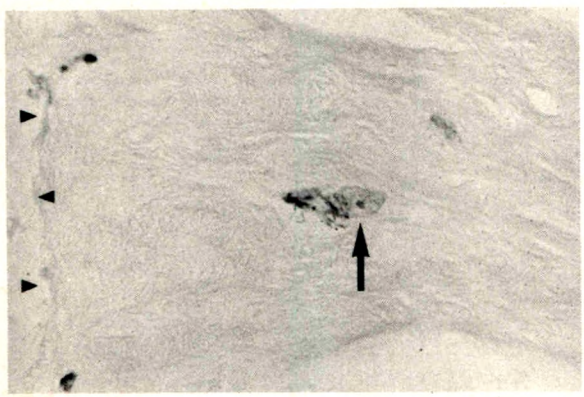


Fig. 10 (Dugel and associates). Case 2. Acid-fast rods are packed within a stromal cell (arrow) adjacent to the margin of resection (arrowheads) (modified Ziehl-Neelson, ×630).

Three months after the initial injury visual acuity was L.E: 20/200. There was a 1 × 3-mm corneal epithelial defect involving the visual axis with an underlying irregularly shaped infiltrate extending deep into the cornea. There were 2+ anterior chamber cells with many fine keratic precipitates. Debridement of the infiltrate to the base of the ulcer produced no foreign body residues. *Mycobacterium fortuitum* grew 15 days after scrapings were placed on Lowenstein-Jensen media. The organisms were sensitive to ethionamide and partially sensitive to kanamycin and streptomycin, but antibiotic therapy was not initiated. Debridement of the ulcer was repeated several times over a six-week period. The corneal epithelium healed over a faint anterior stromal scar. The surrounding cornea remained clear and the eye quiet. Visual acuity was L.E.: 20/20 four years after the initial injury.

Discussion

Mycobacterium fortuitum is a nontuberculous, acid-fast bacillus that has been classified by Runyon[1] as a Group IV, or rapid-growing, mycobacterium on the basis of its culture characteristics.[13] It was first isolated from a postinjection abscess and named by Cruz in 1938.[14] *Mycobacterium fortuitum* may cause a variety of infections, including tuberculosis-like disease of the lungs, cellulitis, soft-tissue abscesses, lymphadenitis, and keratitis.[2,3,14]

Mycobacterium fortuitum is found in soil and water,[9,13] and has been isolated from sputum and saliva,[15] gastric contents,[2] and the ocular surface (B. J. Mondino, M.D., oral communication, February 1988) of apparently healthy individuals. Inoculation probably occurs in most cases by contaminated foreign bodies, needles, or injectable material, but some infections in immunocompromised patients may be of endogenous origin.[13]

Mycobacterium fortuitum is closely related to *M. chelonei*, another cause of corneal disease.[16,17] The two species were recognized as distinct organisms only in 1972.[18,19] *Mycobacterium fortuitum* can be distinguished from *M. chelonei* on the basis of positive iron uptake and nitrate reduction tests. Because the two species have a similar disease spectrum, they may have been confused in earlier disease reports. Those cases of atypical mycobacterial keratitis, in which the organism was specifically identified as *M. fortuitum*, are summarized in the Table. There are no obvious racial or geographic predilections for infection. Patients were not described as having preexisting systemic diseases that might alter host defenses.

Mycobacterium fortuitum keratitis is associated most frequently with foreign body injuries. At least nine of the 12 previously reported cases, and one of the four current cases, followed such trauma. No single type of foreign body was associated with these injuries, but many were from dirty environments, indicating that they could have been contaminated with *M. fortuitum*. Infection of traumatized corneas may occur secondarily in some cases. Although keratitis apparently developed immediately in cases reported by Sexton[8] and Turner,[9] it was not recognized for periods as long as two months in others.[4,5,7,11]

Infection was associated with contact lens wear in three of the current cases. It was not determined whether organisms were introduced via contaminated lenses or whether secondary infections developed in corneas compromised by contact lens-associated hypoxia or microtrauma.

Two of the patients in our study had had surgical procedures that may have further compromised host defenses. Wunsch and associates[7] also described *M. fortuitum* keratitis in a corneal graft. Suture removal probably allowed access of organisms to the cornea.

Lazar and associates described early signs of infection in four patients, which they believe to be characteristic of *M. fortuitum* keratitis.[11] Thin white stromal plaques with radiating lines resembling a cracked windshield were present

TABLE

CHARACTERISTICS OF *MYCOBACTERIUM FORTUITUM* KERATITIS IN REPORTED CASES

STUDY	INSULT TO CORNEA	INTERVAL BETWEEN INJURY AND KERATITIS	ANTIMYCOBACTERIAL THERAPY ATTEMPTED†	CORTICO-STEROIDS USED IN TREATMENT	DURATION OF DISEASE ACTIVITY (MOS)
Turner and Stinson[4]	Metallic foreign body	2 mos	Streptomycin, kanamycin Neomycin-polymyxin B-gramicidin	Yes	2
Levenson and Harrison[5]	Metallic foreign body	2 wks	None	Yes	6
Zimmerman, Turner, & McTigue*[6]	Preexisting chronic keratopathy of unknown cause	Unknown	None	Yes	8–12
Wunsh and associates[7]	Surgery, suture removal	2 wks	Kanamycin Neomycin-polymyxin B-gramicidin	Yes	6
Sexton[8]					
Case 1	Clay foreign body	Immediate	Streptomycin, isoniazid (oral) Para-aminosalicylic acid (oral)	Unknown	5
Case 2	Unknown foreign body	Immediate	Streptomycin, isoniazid (oral) Para-aminosalicylic acid (oral)	Unknown	2
Turner[9]	Unknown foreign body	Immediate	Neomycin-polymyxin B-bacitracin	Yes	1
Willis and Laibson[10]	Flash burn	Unknown	Kanamycin	Yes	5–10
Lazar and associates[11]					
Case 1	Unknown foreign body	2 wks	Streptomycin, kanamycin	Yes	10
Case 2	Unknown foreign body	2 wks	Streptomycin, kanamycin	Yes	13
Case 3	Unknown foreign body	2 wks	Rifampin (topical and oral)	Yes	5
Case 4	Unknown foreign body	3 wks	Rifampin (topical and oral)	Yes	6
Present study					
Case 1	Contact lens	Unknown	Amikacin	Yes	6
Case 2	Surgery, contact lens	Unknown	Amikacin, doxycycline (oral)	Yes	18
Case 3	Surgery, contact lens	Unknown	Amikacin	Yes	Unknown
Case 4	Foreign body	3 mos	None, treated by debridement	At time of injury only	6

*Report also includes the patient described by Wunsh and associates.[7]

†Topical unless otherwise indicated.

‡Not applicable.

§Recurrent retinal detachment.

TABLE (*Continued*)

REPORTED OUTCOME	FINAL VISUAL ACUITY
"Healed" ulcer	Not reported
Resolution after lamellar keratoplasty	20/50+2
Spontaneous perforation, enucleation	N.A.‡
Opaque, vascularized cornea	Light perception
"Inactive" ulcer	20/30
Resolution	20/80
'Healed" ulcer	Not reported
Quiescence of inflammation	Not reported
Inactive corneal scar	20/200
Inactive corneal scar	20/200
Inactive corneal scar	20/40
Inactive corneal scar	20/40
Corneal thinning, penetrating keratoplasty	20/30
Persistent infiltrates, penetrating keratoplasty	Light perception§
Quiescent, opaque cornea	Counting fingers
Clear cornea	20/20

for two to three days before development of large, dense stromal infiltrates. These early changes were not recognized in the current cases.

Multiple anterior and deep stromal infiltrates were present in many of the current and previously reported cases, resulting in frequent misdiagnoses of stromal herpes simplex virus keratitis or fungal keratitis.[4,6-8,10]

Mycobacterium fortuitum keratitis follows an indolent course in most cases. Corneal inflammation may wax and wane for many months. Exacerbations are frequently associated with hypopyon.[6,8-11] Pain is variable. Regardless of the therapy used, infection eventually resolved in most cases leaving an opaque scarred cornea that reduced vision. The infection may be more fulminant in certain cases. The patient described by Zimmerman, Turner, and McTigue[6] required enucleation after spontaneous perforation of the cornea. In our Case 1 penetrating keratoplasty was required for treatment of rapid corneal thinning.

Corticosteroid therapy may be one factor that adversely affects the course of disease. Although corticosteroid therapy may cause transient improvement in inflammation, it probably contributes to disease chronicity. In at least ten of the previously reported 12 cases the patients were treated with corticosteroids. In the remaining two, corticosteroid therapy was not specifically mentioned. In the current series, rapid progression of corneal thinning in Case 1 followed initiation of topical corticosteroid therapy. The only patient who did not develop extensive disease and loss of vision (Case 4) was the only one not treated with a course of topical corticosteroids.

Mycobacterium fortuitum keratitis is characterized histopathologically by ulceration with corneal stromal necrosis and a variable inflammatory infiltrate.[5,6] Acid-fast organisms can be demonstrated in macrophages, keratocytes, and within the stromal extracellular matrix. Examination of the penetrating keratoplasty specimens in Cases 1 and 2 disclosed disparate responses to *M. fortuitum* infection. In Case 1, the patient had ulceration and marked stromal necrosis with a predominantly acute inflammatory infiltrate, similar to that reported by Zimmerman, Turner, and McTigue.[6] Acid-fast bacilli were found both intracellularly and extracellularly within the stroma (Figs. 4 and 5). Case 2 was a different histopathologic picture. The initial donor tissue displayed occasional sparsely populated aggregates of mononuclear

cells and granular extracellular material scattered throughout an otherwise noninflamed stroma (Figs. 7 and 8). No areas of ulceration or necrosis were present. Acid-fast rods were profusely abundant within the aggregates, primarily extracellularly. In the rim of host tissue also removed, a dense perivascular lymphocytic infiltrate was present at the donor-host interface (Fig. 9). Acid-fast organisms also were observed in the host stroma, although in far fewer numbers. Even in the second donor graft, rare acid-fast bacilli were discovered within keratocytes adjacent to the wound margin, again without a significant inflammatory response (Fig. 10). The reason for a lack of inflammatory response in the donor tissues is unclear. Possible factors include its avascularity, corticosteroid and antibiotic therapy, or nonviability of organisms.

Mycobacterium fortuitum was identified by culture of corneal scrapings in 14 of 16 cases. Cultures for acid-fast bacilli were not performed initially in the other two but organisms were identified later in surgical specimens.[5,6] *Mycobacterium fortuitum* will grow, albeit slowly, on a variety of standard culture media. It grows rapidly, however, on specific mycobacterial media such as Lowenstein-Jensen, usually producing visible colonies at 37 C or room temperature in two to three days.

The appearance of *M. fortuitum* in culture has been confused frequently with *Nocardia asteroides*,[4,6,8,10] which also is capable of producing an acute necrotizing keratitis. They may be differentiated by appropriate staining techniques.[6] *Nocardia asteroides* is a delicate, branched, filamentous organism 10 to 20 μm long that is weakly acid-fast and gram-positive. *Mycobacterium fortuitum* is a pleomorphic organism 1 to 4 μm long that is strongly acid-fast and easily missed by Gram staining. Neither organism can be identified on specimens stained by hematoxylin and eosin.

A variety of antibiotics were used for treatment in the reported cases. *Mycobacterium fortuitum* usually is resistant to most antibiotics, including standard antituberculosis drugs. Even with in vitro evidence of kanamycin sensitivity, no in vivo response to the drug was noted in one case.[10] In vitro sensitivity to neomycin was reported for one isolate.[4] Many of the patients were given neomycin preparations at some point in the course of their disease. Whether or not this drug affected the outcome of infection is not known.

Dalovisio and associates[12] reported successful treatment of *M. chelonei* keratitis and nonocular *M. fortuitum* infections with amikacin. The minimum inhibitory concentrations range from 0.25 mg/ml to 4.00 mg/ml for *M. chelonei* and 0.25 mg/ml to 1.00 mg/ml for *M. fortuitum*.[20] On the basis of their experience, three of the patients in our series were treated with topical amikacin. In each the concentration of amikacin was greater than the 10-mg/ml topical solution used by Dalovisio and associates for *M. chelonei* keratitis. In our Case 1 a 50-mg/ml topical solution was used with no clinical response. In Cases 2 and 3, a 100-mg/ml topical solution was used with clinical evidence of disease response in both patients. In Case 2, however, organisms were found still to be present in the host corneal tissue after penetrating keratoplasty one month later. In Case 3, pathologic confirmation of treatment efficacy was not obtained. It is, therefore, difficult to interpret the results of amikacin therapy.

Subsequent in vitro testing of isolates in Case 1 showed them to be sensitive to ciprofloxacin, a new fluoroquinolone antimicrobial agent, which inhibits bacterial DNA gyrase, an enzyme essential for DNA replication.[21] Ciprofloxacin has in vitro activity against a broad spectrum of organisms including *M. fortuitum*.[22] Ciprofloxacin was not available for clinical use at the time the patient was treated. The drug should be investigated further for possible use in treatment of mycobacterial keratitis.

Extirpation therapy has been advocated for treatment of nonocular *M. fortuitum* infections. Surgical removal of organisms from infected corneas also appears to be beneficial. Patients described by Levenson and Harrison[5] and Wunsch and associates[7] improved after removal of infected tissue by keratotomy. Despite failure of medical therapy in our Case 1, there was no evidence of recurrent infection after penetrating keratoplasty. Although organisms were present in corneal tissue when penetrating keratoplasty was performed in Case 2, the graft has remained clear. In Case 4 mechanical debridement was used successfully. The nontuberculous mycobacteria should be considered in cases of indolent keratitis in which the cornea has been previously compromised by trauma, surgery, or disease. Routine acid-fast staining and mycobacterial culture of corneal scrapings are recommended. Most patients with *M. fortuitum* keratitis have eventually required penetrating keratoplasty for visual rehabilitation. In the future, earlier

diagnosis, the avoidance of corticosteroid therapy, and the use of new antibiotics may allow more successful medical management of this disorder.

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Toxic Endothelial Degeneration in Ocular Surface Disease Treated With Topical Medications Containing Benzalkonium Chloride

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We examined a 56-year-old man with keratoconjunctivitis sicca and marked ocular surface disease in whom the prolonged frequent use of topical medications containing the preservative benzalkonium chloride was associated with corneal endothelial damage requiring corneal transplantation in one eye. The histopathologic findings on examination of the excised button were consistent with toxic endothelial disease. Postoperatively, the patient's symptoms continued until the preservative-containing medications were substituted with nonpreserved saline eyedrops.

PATIENTS WITH extensive ocular surface disease are often treated with frequent instillations of ophthalmic medications to prevent desiccation of the ocular surface, enhance lubrication, treat microbial disease, and promote epithelial healing. Most of these preparations contain preservatives, which have been shown to be toxic to the ocular surface.[1] In experimental studies, Gasset and associates[2] showed that topical medications containing preservatives in sufficient concentration and given frequently enough can cause extensive damage to the corneal endothelium. This would be presumed to be more obvious in eyes with disruption of the ocular surface, which would allow greater absorption of the preservatives. Benzalkonium chloride, the most toxic preservative,[1-3] is also the most commonly used preservative for ophthalmic medications in strengths ranging from 0.004% to 0.01%. Concentrations of this magnitude have been shown to be toxic to the corneal endothelium in animal studies.[2] We examined and treated a patient with severe keratoconjunctivitis sicca with extensive ocular surface disease. This patient was treated over an eight-year period with frequent instillations of topical medications containing benzalkonium chloride for extensive disruption of the corneal and conjunctival epithelia. After approximately eight years of treatment, he developed severe limbus to limbus corneal edema in one eye that was assumed to be a consequence of advanced degeneration of the endothelium, and required a penetrating keratoplasty. Herein we describe his clinical history, histopathologic findings of the excised corneal tissue, and subsequent course of what we believe to be a severe toxic endotheliopathy caused by topical benzalkonium chloride.

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Case Report

In 1977 bilateral keratoconjunctivitis sicca was diagnosed in a 56-year-old man. He was treated with frequent topical instillations of artificial tears and antibiotics in both eyes. Both of these substances contained benzalkonium chloride as a preservative in a concentration of 0.004%. He was first referred to our institution in 1978 because of intractable pain, photophobia, and extensive breakdown of the corneal epithelium. At that time, visual acuity was 20/25, without correction, in each eye. Slit-lamp examination disclosed extensive, superficial punctate erosions over the entire corneal surface in the right eye. In the left eye, there were numerous small filaments in the superior portion of the cornea and a 2 × 4-mm erosion of the corneal epithelium near the corneoscleral limbus inferiorly. Schirmer tests showed 1 mm of wetting in each eye at five minutes without topical anesthetic. Bell's phenomenon was in-

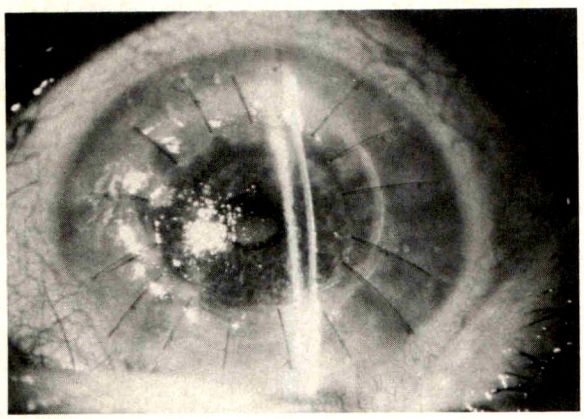


Fig. 1 (Lemp and Zimmerman). Postoperative photograph showing clear penetrating keratoplasty and extensive edema in the host cornea extending to the corneoscleral limbus.

tact bilaterally and there was no evidence of blepharitis. Results of the remainder of the ophthalmologic examination were normal. The patient continued to use artificial tears in both eyes, and was treated with a bandage contact lens to the left eye. Over the next four to six weeks, the corneal erosion in the left eye healed; however, he subsequently developed an erosion in the right cornea, which was also treated with a bandage lens.

Over the next several years he continued to use artificial tears containing benzalkonium chloride throughout the day, white petrolatum-mineral oil ointment several times a day, and hydroxypropyl cellulose. He developed several intercurrent episodes of bilateral blepharitis, which were treated with systemic tetracycline. During this time, he continued to complain of severe bilateral photophobia. His visual acuity varied, depending on the condition of the corneal epithelium. In 1981 a slight pannus was noted inferiorly in the cornea of the left eye, and visual acuity had decreased to 20/50 in that eye. By 1983 visual acuity was 20/70 in the left eye. This decrease was attributed to more severe, central ocular surface disease. By 1984 he had confluent superficial punctuate erosions in the left cornea. He was referred for neuro-ophthalmologic examination because of blepharospasm as a possible cause of or contributing factor to his surface disease; no specific treatment was recommended. In 1984, for the first time, significant corneal edema was observed in the left eye, and his visual acuity had decreased to 20/200. Limbal to limbal epithelial and stromal edema were present. The right eye showed no evidence of edema, but specular microscopy demonstrated a significantly low endothelial cell density (900 cells/mm^2) with extensive polymegethistic changes; no discernible cell outlines were seen in the left eye. No cornea guttata excrescences were observed in Descemet's membrane of either eye.

In 1985 he underwent an 8-mm penetrating keratoplasty in the left eye without complication. The subsequent clinical course was good, with gradual healing of the graft (Fig. 1). Visual acuity improved to 20/30 in that eye. His postoperative medications included frequent bilat-

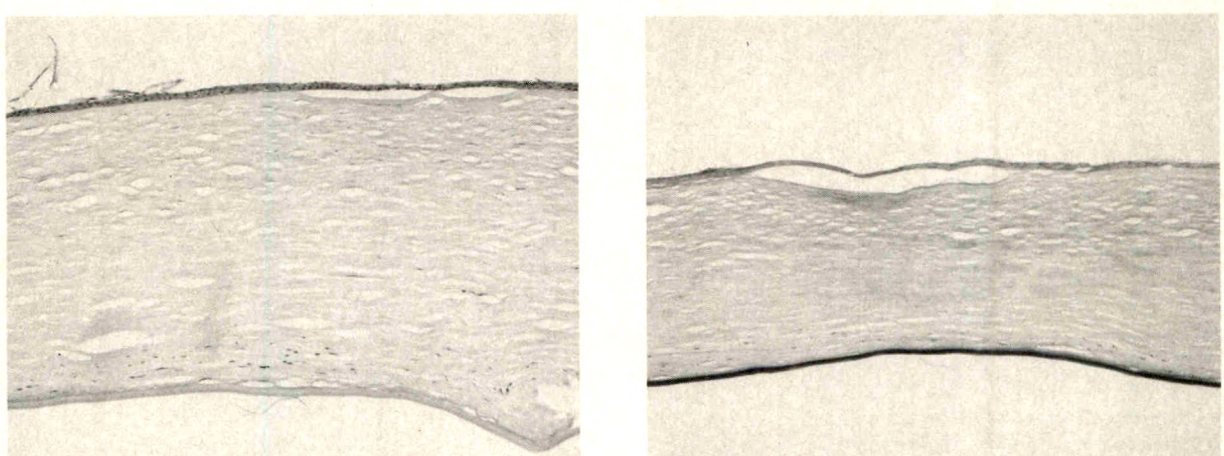


Fig. 2 (Lemp and Zimmerman). The atrophic corneal epithelium exhibits focal bullous detachments from Bowman's layer. Much of the stroma, especially in the deeper layers, is acellular except for the band-like infiltrate of polymorphonuclear leukocytes just anterior to Descemet's membrane (left: hematoxylin and eosin, ×100; right: periodic acid-Schiff, ×75).

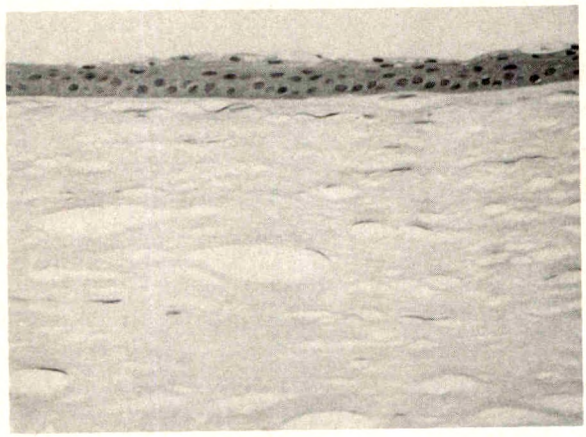


Fig. 3 (Lemp and Zimmerman). An area where Bowman's layer is missing and replaced by a mild proliferation of fibroblasts (hematoxylin and eosin, ×300).

eral instillations of artificial tears, a topical corticosteroid preparation containing benzalkonium chloride, hydroxypropyl cellulose and white petrolatum-mineral oil ointment at night. He continued to complain of severe bilateral photophobia, despite the improvement of his vision. In 1986 the benzalkonium chloride-containing artificial tear was replaced with a nonpreserved saline eyedrop. Within two weeks, he noticed a dramatic improvement in his photophobia and his ability to open his eyes at ease. Small, fine filaments and superficial punctate erosions, which had been present on the surface of both eyes, disappeared. All medications were tapered and then discontinued except for the nonpreserved artificial tears. Visual acuity is currently R.E.: 20/30−2 without correction and L.E.: 20/30+2 with correction. No further changes have been observed in the right eye over a two-year period. There is no evidence of cornea guttata in either eye.

Pathologic findings—The 8-mm corneal button was received in formalin. Histologic sections showed minimal thickening, but pathologic changes consistent with chronic edema were observed in all principal layers. In several places, the atrophic epithelium was separated from Bowman's layer (Fig. 2), while in other areas Bowman's layer was absent and replaced by a small amount of scar tissue (Fig. 3). Keratocytes were missing or markedly atrophic and there was partial homogenization of the collagenous lamellae throughout much of the stroma (Figs. 2 and 4). Descemet's membrane was moderately thickened, which was attributed to a layer of newly formed basement membrane deposited on the original Descemet's membrane (Fig. 5). No cornea guttata excrescences were observed. The friable membrane appeared extremely degenerated. Endothelial nuclei were markedly reduced in number and were tiny and flattened.

Discussion

This case presents convincing evidence of the causative role of benzalkonium chloride in the endothelial degeneration observed both clini-

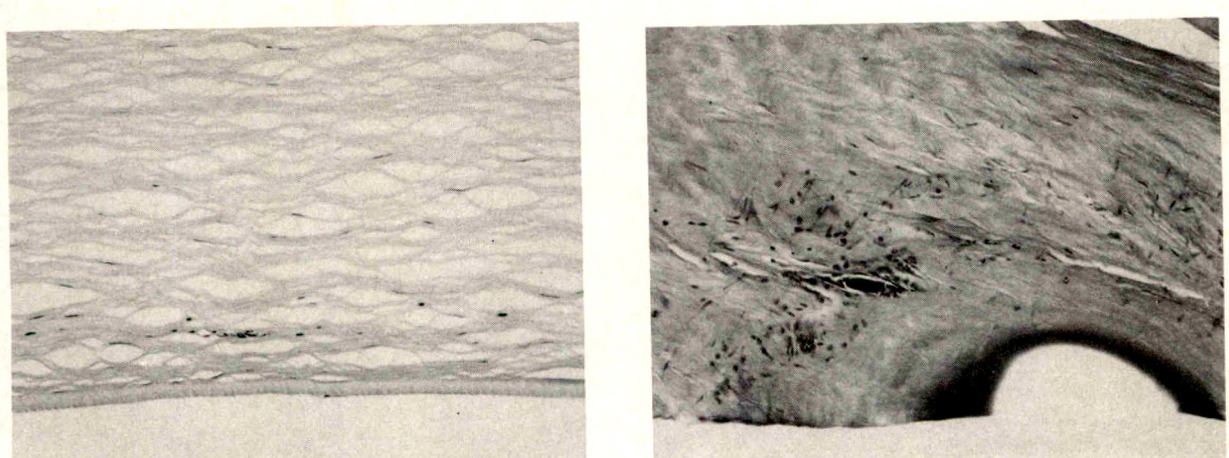


Fig. 4 (Lemp and Zimmerman). The middle and deeper layers of corneal stroma are largely acellular, reflecting a loss of keratocytes. Capillaries and a light infiltrate of polymorphonuclear leukocytes are present just anterior to Descemet's membrane. A few degenerated endothelial cell nuclei can be seen in the extremely attenuated endothelium (hematoxylin and eosin: left, ×200; right, ×300).

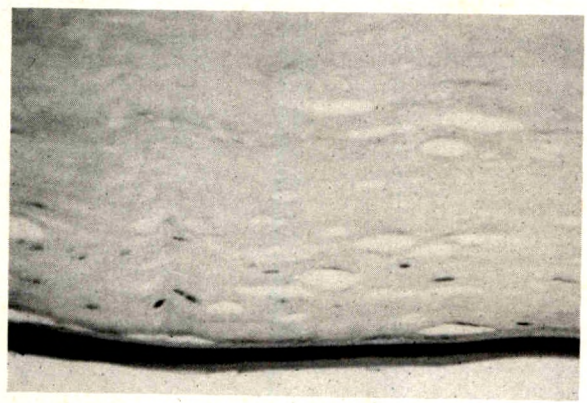


Fig. 5 (Lemp and Zimmerman). A layer of newly formed basement membrane accounts for the slight thickening of Descemet's membrane (periodic acid-Schiff, ×300).

cally and on histopathologic examination.

The postoperative clinical course in this patient was characterized by a continuation of symptoms until the preservative-containing eyedrops were discontinued. On discontinuation, the symptoms were promptly ameliorated. This, together with the absence of cornea guttata in either eye and the histopathologic findings, suggests a toxic process involving the endothelium. Histologically there was neither the significant diffuse thickening nor the cornea guttata excrescences that would be expected with Fuchs' dystrophy or other types of primary endothelial cell disease. The evidence of inflammation with a polymorphonuclear cell infiltrate and vascularization are consistent with a toxic process, but not with Fuchs' dystrophy.

These findings point out the potential danger of prolonged use of topical medications containing benzalkonium chloride as a preservative in the presence of extensive disruption of the corneal epithelium. The availability of nonpreserved saline eyedrops in unit dose dispensers should reduce the incidence of this type of complication. Caution is urged in the use of preservative-containing topical medications over an extended period in patients with extensive ocular surface disease.

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OPHTHALMIC MINIATURE

The following is the voice of Merlin, King Arthur's mentor:

I had certainly perfected the art of melting into a landscape: what I did in fact was assume the tools of some trade, and then frequent places where no one would expect a prince to be. Men's eyes are focused on what, not who, a traveller is, who goes labelled with his skill. I had travelled as a singer when I needed access to a prince's court as well as a humble tavern, but more often I went as a travelling physician or eyedoctor. This was the guise I liked best. It allowed me to practice my skill where it was most needed, among the poor, and it gave me access to any kind of house except the noblest.

Mary Stewart, *The Last Enchantment*
New York, Ballantine Books, 1979, p. 96

Use of an Angiotensin Converting Enzyme Inhibitor in Ocular Hypertension and Primary Open-Angle Glaucoma

William H. Constad, M.D., Philip Fiore, M.D., Cesar Samson, M.D., and Alfonse A. Cinotti, M.D.

We studied the effects of a new topical angiotensin converting enzyme inhibitor, SCH 33861, in lowering intraocular pressure in 20 patients with ocular hypertension or primary open-angle glaucoma. In a double-masked, four-way crossover study with placebo and timolol, SCH 33861 was well tolerated and effective in lowering intraocular pressure. The magnitude of the drug's effect in lowering intraocular pressure was less than that of timolol 0.5%.

Several systemic antihypertensive agents (clonidine, thymoxamine, corynanithine, guanethidine, and the beta-adrenergic blocking agents) when administered topically to the cornea have been effective in reducing intraocular pressure in patients with primary open-angle glaucoma.[1-4] However, with the exception of some of the beta-blockers (timolol, levobunolol, and betaxolol), these agents have all been associated with either systemic or local adverse side effects.

SCH 33861, a potent and reversible inhibitor of angiotensin converting enzyme, was developed by the Schering Corporation. Its chemical name is 7-(N-[1(S)-(Carboxy)-3-phenylproyl]-(S)-alanyl)-1,4-dithia-7-azaspirol[4,4] nonane-8(S)-carboxylic acid hemihydrate. Its molecular weight is 447.6. Initial preclinical studies included topical, oral, and intravenous administration to dogs. There was rapid, but limited gastrointestinal absorption in dogs, and following intravenous administration, 99% of the drug was recovered unchanged in the urine. Thirty-day acute toxicity studies in rats, mice, and dogs following intravenous administration of 10 mg/kg of body weight in rats and mice and 4 mg/kg of body weight in dogs produced no adverse clinical signs or gross histologic changes. Ocular irritation studies showed mild ocular irritation with six times a day dosing both with SCH 33861 in a vehicle and the vehicle by itself.

Based on initial findings of reduced intraocular pressure in normal New Zealand white rabbit eyes (unpublished data, Schering study), we performed this study to investigate the potential effects of SCH 33861 on intraocular pressure in patients with primary open-angle glaucoma or ocular hypertension.

Material and Methods

We conducted a double-masked, four-way crossover study comparing the effects of SCH 33861 0.1% and 0.01% ophthalmic solution, its vehicle as a placebo, and 0.5% timolol. Each crossover phase of the study consisted of five days of treatment followed by a two-day washout period. Twenty patients with bilateral ocular hypertension or primary open-angle glaucoma, aged 21 years or older, were entered into the study. The purpose and methods of the study were explained to each patient and each gave informed consent. The study took place at the Eye Institute of New Jersey in Newark, New Jersey.

Patients underwent a complete ophthalmic examination and were entered into the study if they had either bilateral primary open-angle glaucoma or ocular hypertension with an untreated intraocular pressure of greater than 25 mm Hg. Patients with aphakic glaucoma, end-stage glaucoma, and the secondary glaucomas, including angle closure glaucoma, were excluded from the study. Glaucoma patients whose intraocular pressure could not be controlled by medical therapy alone or any patient who had undergone laser trabeculoplasty were also excluded.

Patients were studied for a period of four

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weeks, during which time they were treated with each one of the four test preparations for a period of five days. Patients who were considered candidates and were already under treatment were requested to withhold antiglaucoma therapy for one week before returning for their initial baseline examination. The baseline (pretreatment) measurements were collected on the morning of day 1 of each week of the four weeks (phases) of the study. The baseline examination consisted of applanation tonometry, pupillometry, determination of visual acuity (near and distance), slit-lamp and ophthalmoscopic examinations, and pulse rate and systemic blood pressure measurements. One drop of the test medication was instilled into each eye, and the following measurements were repeated: applanation tonometry and slit-lamp examination at two, four, eight, 12, and 24 hours after the initial dose; pupillometry at two, four, and eight hours after the initial dose; pulse and systemic blood pressure measurements at two and four hours after the initial dose; and visual acuity at 24 hours after the initial dose.

At the end of the first 24 hours, all patients were instructed to continue treatment with a dose of one drop twice daily to each eye every 12 hours for the next three days. On the morning of the fifth day, all patients again returned for a final dose. Again, measurements were collected according to the same schedule as that of the first day. All medications were then discontinued for the next two days (the washout period), to allow the intraocular pressure to return to baseline levels of ≥25 mm Hg. Patients then returned for another baseline examination and the start of the crossover phase. This same procedure was repeated for each of the four weeks of the study. Statistical significance was determined by using the *t*-test for multivariate analysis.

Results

The study consisted of 20 patients, ten men and ten women, 13 of whom had bilateral primary open-angle glaucoma and seven of whom had ocular hypertension. The average age was 61 years (range, 38 to 72 years). The results of the intraocular pressure changes during the 24 hours of day 1 and day 5 for each of the different medications are shown in Table 1 (day 1) and Table 2 (day 5).

The average intraocular pressure at baseline (day 1, hour 0 of each crossover leg) was not significantly different among the four treatments (26.2 and 27.1 mm Hg for SCH 33861 0.1% and 0.01%, 26.0 mm Hg for placebo, and 26.7 mm Hg for timolol 0.5%; $P = .54$).

After drug administration, SCH 33861 0.01% showed generally greater reduction in intraocular pressure than placebo on day 1, and significantly greater reduction at several time points during 0 to 12 hours on day 5 ($P < .05$). For example, the mean change from baseline on day 5, hour 2 was −2.7 mm Hg for SCH 33861 0.1%, −4.4 mm Hg for SCH 33861 0.01%, and 0 mm Hg for placebo. The average intraocular pressure (Tables 3 and 4) for SCH 33861 0.01% was 24.2 mm Hg on day 1 for an overall drop of 2.9 mm Hg, whereas on day 5 it was 21.5 mm

TABLE 1
AVERAGE INTRAOCULAR PRESSURES ON DAY 1 (AFTER A SINGLE DOSE) (MM HG)

	INTRAOCULAR PRESSURE				
TIME	SCH 33861 0.1%	SCH 33861 0.01%	PLACEBO	TIMOLOL 0.5%	POOLED S.D.
0 hrs	26.2	27.1	26.0	26.7	±2.7
2 hrs	24.5	25.9	24.9	18.4	±3.1
(Change)	(−1.7)	(−1.2)	(−1.1)	(−8.3)	±3.4
4 hrs	23.5	24.7	23.8	18.4	±4.0
(Change)	(−2.7)	(−2.4)	(−2.2)	(−8.3)	±3.2
8 hrs	22.6	24.6	23.9	19.1	±3.7
(Change)	(−3.6)	(−2.5)	(−2.1)	(−7.6)	±3.1
12 hrs	21.7	24.3	21.6	18.6	±3.6
(Change)	(−4.5)	(−2.8)	(−4.4)	(−8.1)	±3.1
24 hrs	23.7	25.4	25.0	21.9	±3.5
(Change)	(−2.5)	(−1.7)	(−1.0)	(−4.8)	±3.5

TABLE 2
AVERAGE INTRAOCULAR PRESSURES ON DAY 5 (AFTER FOUR DAYS OF TWICE A DAY INSTILLATION)
(MM HG)

	INTRAOCULAR PRESSURE				
TIME	SCH 33861 0.1%	SCH 33861 0.01%	PLACEBO	TIMOLOL 0.5%	POOLED S.D.
0 hrs	23.9	24.9	26.0	20.8	±3.3
(Change)	(−2.3)	(−2.2)	0.0	(−5.9)	±3.8
2 hrs	23.4	22.9	25.8	19.2	±3.0
(Change)	(−2.8)	(−4.2)	(−0.2)	(−7.5)	±4.0
4 hrs	22.6	23.7	25.0	19.8	±3.5
(Change)	(−3.6)	(−3.4)	(−1.0)	(−6.9)	±4.0
8 hrs	22.0	21.8	24.9	18.4	±3.6
(Change)	(−4.2)	(−5.3)	(−1.1)	(−8.4)	±4.2
12 hrs	20.2	20.4	21.9	18.3	±2.2
(Change)	(−6.0)	(−6.7)	(−4.1)	(−8.4)	±3.1
24 hrs	23.1	24.6	25.0	20.9	±3.9
(Change)	(−3.1)	(−2.5)	(−1.0)	(−5.8)	±4.2

Hg for an overall drop of 5.6 mm Hg. For timolol 0.5% the average was 19.3 mm Hg for an overall drop of 7.4 mm Hg on both day 1 and day 5. As compared to timolol 0.5%, SCH 33861 (0.1% and 0.01%) and placebo were significantly less effective in reducing mean intraocular pressure at virtually all time points ($P < .01$). No statistically significant differences were detected between SCH 33861 0.1% and 0.01% ($P < .05$), except for day 1 at 12 hours (mean change, −4.8 mm Hg for SCH 33861 0.1% and −2.6 mm Hg for SCH 33861 0.01%; $P = .05$).

There were no consistent or significant changes noted in results of pupillometry or visual acuity measurements during the study.

There were no statistically significant differences in systolic and diastolic blood pressure measurements for any of the drugs given. Pulse rate, however, was significantly decreased with timolol 0.5%. The decrease ranged from 6.1 to 11.0 beats/minute ($P < .05$). There was no statistically significant change in pulse rate from baseline seen with either SCH 33861 0.1% or 0.01% or placebo.

There were few reported adverse reactions during the four-week study. While taking SCH 33861 0.1%, one patient complained of mild dizziness that lasted one week. Another patient complained of "foreign body sensation" and "burning sensation" while taking placebo. Five patients developed mild conjunctival injection or superficial punctate keratitis or both during the study. Probable adenovirus infection was subsequently diagnosed in these patients. It was not believed to be related to the drug treatment and all five patients completed the study. The diagnosis was based on results of slit-lamp examination and the presence of tender preauricular nodes. No viral studies were performed on either the patients or drugs. All cases resolved completely without sequelae.

TABLE 3
AVERAGE INTRAOCULAR PRESSURES
AT 0 TO 12 HOURS, DAY 1
(MM HG)

DRUG	AVERAGE INTRAOCULAR PRESSURE (0–12 HRS)*	CHANGE (FROM DAY 1, HR 0)
SCH 33861 0.1%	22.9	−3.3
SCH 33861 0.01%	24.2	−2.9
Placebo	23.5	−2.5
Timolol 0.5%	19.3	−7.4

*Pooled S.D. = ±3.5 mm Hg.

TABLE 4
AVERAGE INTRAOCULAR PRESSURES AT
0 TO 12 HOURS, DAY 5
(MM HG)

DRUG	AVERAGE INTRAOCULAR PRESSURE (0–12 HRS)*	CHANGE (FROM DAY 1, HR 0)
SCH 33861 0.1%	21.7	−4.5
SCH 33861 0.01%	21.5	−5.6
Placebo	24.3	−1.8
Timolol 0.5%	19.3	−7.4

*Pooled S.D. = ±3.0 mm Hg.

Discussion

Angiotensin converting enzyme inhibitors are potent antihypertensive agents. In New Zealand white rabbits, the administration of 50 μl of SCH 33861 0.01% in a hydroxypropylmethyl cellulose vehicle reduced intraocular pressure by 5.6 ± 0.4 mm Hg ($P < .05$) from basal levels of about 20 mm Hg (unpublished data, Schering study). The ocular hypotensive effect lasted at least four hours. Higher concentrations of up to 1% proved no more efficacious. In combination with topical timolol 0.5%, peak intraocular pressure reduction with SCH 33861 0.01% was 6.2 ± 0.6 mm Hg ($P < .05$). In all concentrations, the combined effect was significantly greater than that with either drug alone. Studies were also undertaken to evaluate the duration of action. Two different vehicles were used and intraocular pressure was measured for 24 hours after a single dose of SCH 33861 0.1% and 0.01%. This was done in an attempt to measure possible increased ocular penetration. Timolol produced a comparable peak reduction in intraocular pressure at two hours, with a gradual return to baseline; there was a significant effect at 12 hours but none at 24 hours.

Angiotensin converting enzyme activity is present in aqueous humor[5,6] and its level is increased in sarcoid granulomatous inflammations.[7,8] The actions of angiotensin converting enzyme activity in the aqueous humor or its mechanism of production are unknown. It has been suggested that blood flow to the optic nerve via the posterior ciliary arteries may be directly responsive to angiotensin I,[8] and angiotensin I may play a role in blood flow to the ocular vascular beds. The vasoconstrictive action of angiotensin I on ocular vasculature may shunt blood to the ciliary body. This could increase the metabolic activity and thus the production of aqueous humor by the ciliary body.

Our results showed that SCH 33861 was well tolerated topically and at least in the short term, had much fewer systemic effects, especially on heart rate, than timolol 0.5%. SCH 33861 lowered intraocular pressure significantly in our study. It is of interest that for SCH 33861, the decrease in intraocular pressure was greater on day 5 than on day 1. This suggests that there is at least a partial cumulative effect on intraocular pressure, similar to the effect seen with pilocarpine as well as other drugs. The magnitude of the decrease in intraocular pressure is not as great as that found with timolol, and its efficacy over the long term has yet to be evaluated. In its present form, angiotensin converting enzyme inhibitor does appear promising as a new drug for the control of intraocular pressure.

Further studies are needed to discover the nature of angiotensin converting enzyme activity in aqueous humor. Perhaps another angiotensin converting enzyme inhibitor would prove even more potent in its effect on intraocular pressure, thus offering a new family of pharmaceutic agents with fewer systemic side effects to the present armamentarium in the treatment of glaucoma.

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Comparison of Intraocular Pressure Measurements With the Oculab Tono-Pen vs Manometry in Humans Shortly After Death

Volker Hessemer, M.D., Ralf Rössler, and Karl W. Jacobi, M.D.

We compared the Oculab Tono-Pen, a miniaturized Mackay-Marg tonometer, with a Statham membrane manometer in six humans (12 eyes), three to six hours after death. The intraocular pressure was changed in 5- to 10-mm Hg steps in a range between 0 and 60 mm Hg by an infusion system. The correlation coefficient of the relation of Tono-Pen readings vs manometrically determined intraocular pressures was .99. Compared to the manometer, the Tono-Pen gave a small underestimation of intraocular pressure above 17 mm Hg or overestimation below 17 mm Hg. The maximal deviation of the Tono-Pen readings from the manometer readings was 2.5 mm Hg. In our experience the correspondence between Tono-Pen and manometer readings was superior to the correspondence between the readings obtained with the original Mackay-Marg tonometer and manometry.

THE OCULAB TONO-PEN is a hand-held tonometer that is similar in operating principle to the Mackay-Marg tonometer.[1-3] Minckler and associates[4] recently performed a clinical evaluation of the Tono-Pen vs the Goldmann applanation tonometer. The intraocular pressure values ranged primarily from 10 to 30 mm Hg. Pressures below and above this range were measured infrequently.

In our evaluation of this new tonometer, we chose a reference instrument that measures intraocular pressure directly and absolutely and compared the two instruments in an intraocular pressure range from 0 mm Hg to the upper limit of clinically observable pressures. These pressures were obtained experimentally in human eyes shortly after death.

Accepted for publication March 4, 1988.

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Material and Methods

The Tono-Pen has been described in detail by Minckler and associates.[4] Briefly, the hand-held, battery-operated instrument is pen-sized (18 cm in length), and weighs about 60 g. Similar to the original Mackay-Marg tonometer,[1-3] the Tono-Pen uses a solid strain gauge transducer. The tip of the Tono-Pen contains a central 1.02-mm diameter plunger that extends 5 μm beyond a surrounding 3.22-mm diameter annulus. When the cornea is flattened against the plunger surface and, immediately thereafter, against the surrounding annulus surface, a typical voltage change is created: initially a steep rise to a crest, then a trough, and a second rise. Usually, a mirror-like voltage change is found when the instrument is withdrawn from the cornea. In the original Mackay-Marg tonometer,[1-3] the height from the baseline to the trough of the voltage curve is measured, which is printed out on a paper tracing. In the Tono-Pen, the voltage change is digitized, stored, and analyzed by a single-chip microprocessor, which has internal algorithms that measure and discriminate the same parameters. Three to six accepted measurements are averaged, and the mean pressure reading is displayed in millimeters of mercury on a liquid crystal display. As a measure of reliability and spread of the single measurements, the range of the coefficient of variance (5%, 10%, 20%, >20%) is also displayed. Before performing a measurement, the Tono-Pen tip is covered with a disposable latex membrane.

We used a commercially available series model of the Tono-Pen. Two of the users (V.H. and R.R.) had been trained in the use of the instrument by manufacturer's representatives.

The measurements were performed in six human subjects (52 to 78 years of age), three to six hours after death in one of the intensive care units of the University of Giessen Medical Center. The subjects had no history of corneal

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diseases or refractive errors greater than ±2 diopters. The eyes were undamaged, and the corneas were clear at the time of measurement. Before each measurement, the informed consent of at least one of the dependents was given. Shortly thereafter, the cadaver with eyes closed was transported to the pathology laboratory, where the measuring devices had been installed. The cadaver was supported in a horizontal position. The eyes were left in situ. A Schott eyelid retractor was inserted into the first eye to be measured. The entire cornea and the limbal region were exposed. The cornea was continuously irrigated with BSS solution except during the Tono-Pen measurements. A sharp 27-gauge, ¾-inch disposable needle was passed through the corneoscleral limbus into the anterior chamber. The needle was connected to a BSS-filled infusion system, which was adjustable in height. A second 27-gauge, ¾-inch needle was inserted into the anterior chamber, also using a limbal approach. The tips of the two needles lay freely in the anterior chamber (about 3 mm from the corneoscleral limbus) and had no contact with adjacent tissues. Via a BSS-filled tubing, the second needle was connected to a Statham membrane manometer consisting of a disposable measuring dome and a pressure transducer. The manometer signal was amplified and recorded on a sensitive multipen recorder. Before each measurement, a calibration curve of the Statham manometer was made using a legally verified calibration membrane manometer. By changing the height of the infusion system, the intraocular pressure was changed in 5- to 10-mm Hg steps ranging from 0 to 60 mm Hg. At each pressure step, a Tono-Pen measurement was made according to the instructions outlined by Minckler and associates.[4] Only those measurements with a variance of 5% were accepted. At manometer pressure readings below 5 mm Hg, it was difficult, and in some cases impossible, to perform Tono-Pen measurements because of the flexible cornea. In each of the six cadavers, both eyes were investigated consecutively.

For statistical analysis, the pressure readings obtained with the Tono-Pen were plotted against the corresponding manometer values. An analysis of variance was performed to test whether a linear relationship between the Tono-Pen and manometer readings could be assumed. Since this hypothesis could be accepted ($P < .001$), a linear regression analysis was performed. A polynomial regression analysis was also performed to obtain the mathematically exact formulation of the relationship between the pressure readings of the two instruments. Furthermore, the differences of the Tono-Pen readings minus the manometer values were calculated. These differences were plotted against the manometer and the Tono-Pen readings, respectively. Thereafter, the same statistics as described above were applied to these plots.

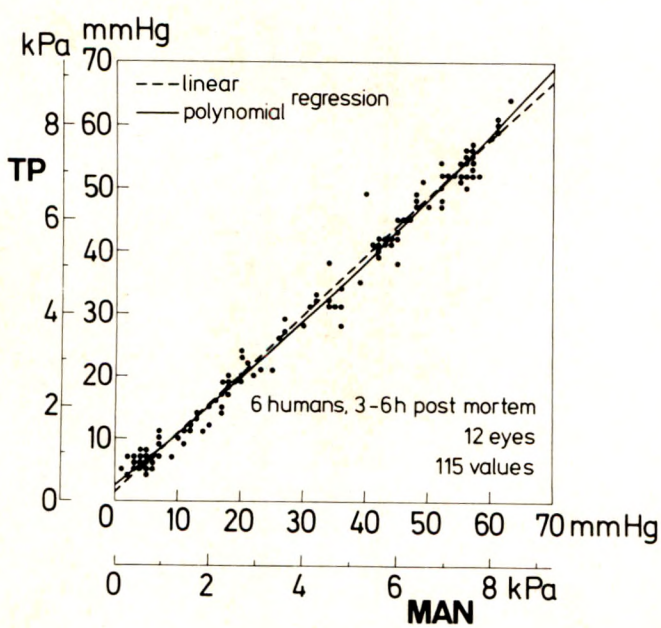


Fig. 1 (Hessemer, Rössler, and Jacobi). Tono-Pen (TP) pressure readings plotted against intraocular pressures measured by manometry (MAN). Several values are plotted repeatedly. Linear and polynomial regression curves are also shown. For regression equations, see the Table.

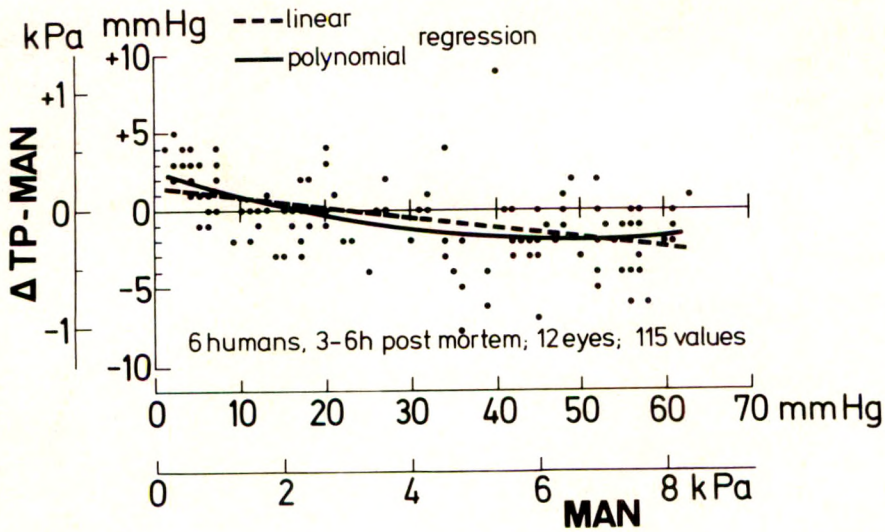


Fig. 2 (Hessemer, Rössler, and Jacobi). Differences of Tono-Pen minus manometer pressure readings (ΔTP − MAN) plotted against intraocular pressures measured by manometry (MAN).

Results

We obtained 115 pairs of values using the Tono-Pen and manometer in a pressure range extending continuously from 1 to slightly above 60 mm Hg (Fig. 1). The linear and polynomial regression curves depicted in Figure 1 are described by the equations given in the Table. The slope of the linear regression curve was 0.94 and the y intercept was 1.46 mm Hg (for comparison, the slope and y intercept of the line of ideal correspondence with manometric values are 1 and 0, respectively). The correlation coefficient was .99. The standard deviation of the Tono-Pen readings in relation to the regression line was 2.36 mm Hg. The mean values of 29.9 (Tono-Pen) and 30.4 mm Hg (manometer) were not significantly different ($P > .05$, analysis of variance). The polynomial regression curve closely approximated the linear curve.

Figure 2 elucidates the systematic deviation between Tono-Pen readings and manometric intraocular pressures. The differences of the Tono-Pen readings minus the manometer values were plotted against the manometric pressures. The correlation coefficient for this relation was −0.46 (see the Table for regression equations). Positive or negative differences suggest that Tono-Pen readings are too high or too low, respectively. For example, at a manometric pressure of 1 mm Hg, the Tono-Pen values are, on an average, 2.5 mm Hg too high, if the exact polynomial curve is considered. At a manometric pressure of 17 mm Hg, there is no

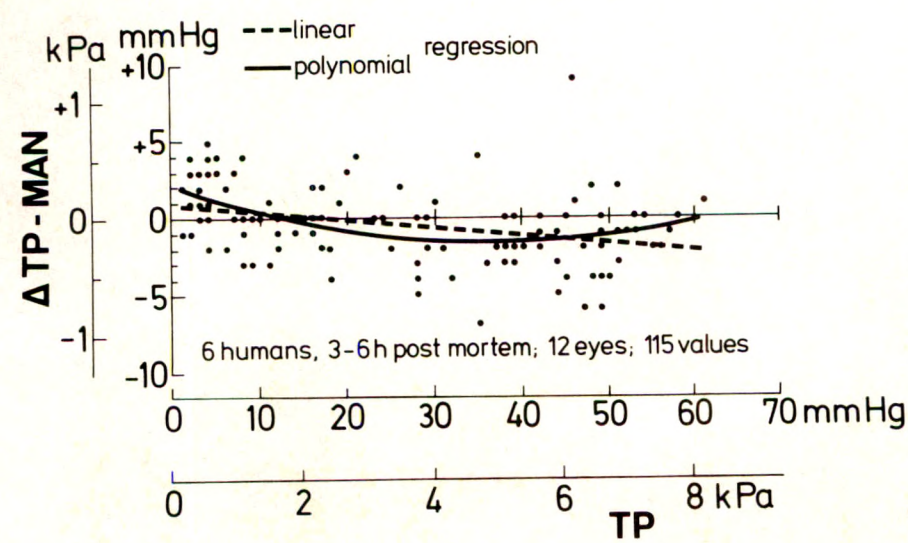


Fig. 3 (Hessemer, Rössler, and Jacobi). Differences of Tono-Pen minus manometer intraocular pressure readings (ΔTP − MAN) plotted against Tono-Pen (TP) pressure readings.

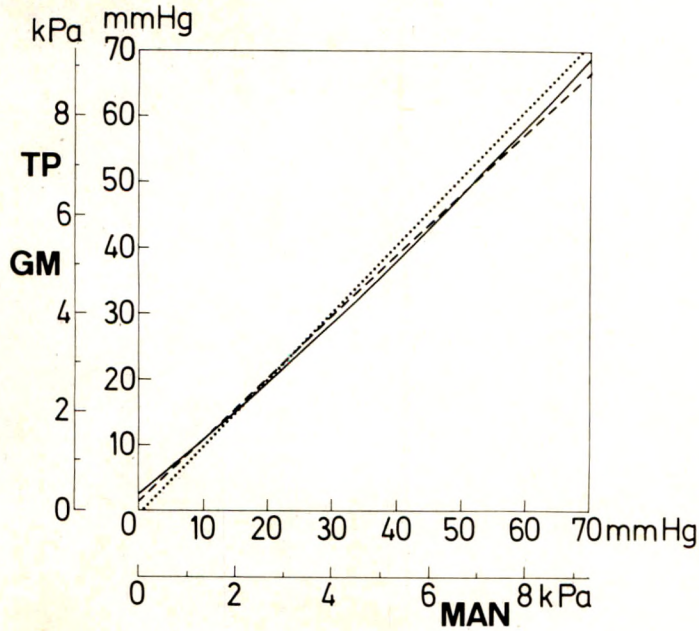


Fig. 4 (Hessemer, Rössler, and Jacobi). Composite diagram comparing the relationship between Tono-Pen (TP) and manometer (MAN) intraocular pressure readings (present results) with relationship between Goldmann tonometric (GM) and manometric readings in enucleated human eyes. Dashed line, linear regression present study; solid line, polynomial regression present study; dotted line, linear regression Goldmann and Schmidt study.

deviation between the two instruments. At a manometric pressure of 60 mm Hg, the Tono-Pen values are, on an average, 2.5 mm Hg too low.

Figure 3 illustrates the mean deviation of a certain Tono-Pen reading from the manometrically measured intraocular pressure. As in Figure 2, the differences of the Tono-Pen readings minus the manometer values were calculated; however, these differences were plotted against the Tono-Pen readings. The correlation coefficient for this relation was −.35 (see Table for regression equations). The curves in Figure 3 slightly deviate from those depicted in Figure 2. For example, when the Tono-Pen user measures 1 mm Hg, the Tono-Pen overestimates the intraocular pressure by an average of 2 mm Hg, related to the polynomial curve. When the user measures 15 mm Hg, this value may be assumed to represent accurately the intraocular pressure. When the Tono-Pen displays values between 25 and 50 mm Hg, these readings underestimate the intraocular pressure by an average of 1 to 1.5 mm Hg. When the Tono-Pen

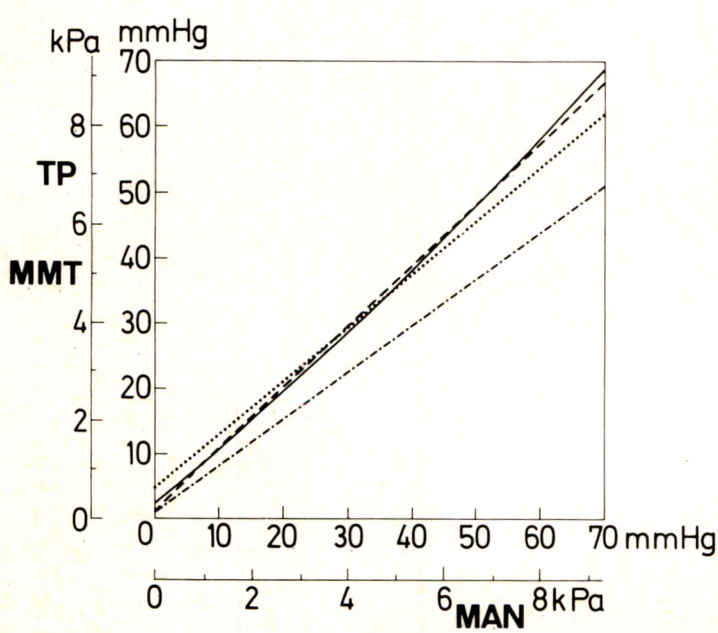


Fig. 5 (Hessemer, Rössler, and Jacobi). Composite diagram comparing the relationship between Tono-Pen (TP) and manometer (MAN) intraocular pressure readings (present results) with relationship between readings of original Mackay-Marg tonometer (MMT) and manometric pressures in enucleated eyes or human cadaver eyes. Dashed line, linear regression present study; solid line, polynomial regression present study; dotted line, linear regression Draeger and Becker study; dashed and dotted line, linear regression Moses, Marg, and Oechsli study.

TABLE
REGRESSION EQUATIONS FOR COMPARISON OF TONO-PEN AND MANOMETER*

PLOT (MM HG)		
Y AXIS	X AXIS	REGRESSION EQUATION
Tono-Pen	Manometer	Linear: $y = 0.94x + 1.46$ Polynomial: $y = 0.82x + 0.002x^2 + 2.52$
Tono-Pen minus manometer readings	Manometer	Linear: $y = -0.06x + 1.46$ Polynomial: $y = -0.18x + 0.002x^2 + 2.52$
Tono-Pen minus manometer readings	Tono-Pen	Linear: $y = -0.05x + 1.03$ Polynomial: $y = -0.22x + 0.003x^2 + 2.70$

*For corresponding curves, see Figures 1 through 3.

readings are in the range of 60 mm Hg, there is no essential deviation from the intraocular pressure, if the exact polynomial curve is considered. The latter point demonstrates that, under certain circumstances, erroneous conclusions may be drawn if linear regression analysis alone is performed.

Discussion

Minckler and associates[4] recently compared the Tono-Pen with Goldmann applanation tonometry in patients from an eye clinic. In comparison to the Goldmann tonometer, the Tono-Pen was found to give a small overestimation of intraocular pressure in eyes with low intraocular pressure or underestimation in eyes with high intraocular pressure. The present study confirmed their results by using a reference instrument that measured intraocular pressure directly and absolutely, that is, a manometer, and by performing continuous measurements in the entire clinically observable intraocular pressure range. This latter condition was achieved by experimentally changing the intraocular pressure in eyes of humans shortly after death. The use of human eyes avoids the difficulties encountered in animal eyes because of the possibility that different corneal anatomy may lead to erroneous tonometric readings.[5]

Comparing the relationship between the Tono-Pen and manometer readings (present results) with the relationship between Goldmann tonometric and manometer readings (results from Goldmann and Schmidt[5] in enucleated human eyes) showed that both the Tono-Pen and the Goldmann readings deviate slightly from the line of ideal correspondence with the manometric values, that is, a line with a y intercept of 0 and slope of 1 (Fig. 4). However, whereas the Tono-Pen gives slightly too high or too low readings in the low or high manometric pressure range, respectively, the Goldmann readings deviate slightly from the manometric pressures in the opposite direction.

Comparing the relationship between the Tono-Pen and manometer readings (present results) with the relationship between the original Mackay-Marg tonometer and manometer readings obtained in enucleated human eyes (results from Moses, Marg, and Oechsli[3]) or in human cadaver eyes (results from Draeger and Becker[6]) demonstrated that the curves describing the Tono-Pen/manometer relationship more closely approximate the ideal line than the curves describing the Mackay-Marg tonometer/manometer relationship (Fig. 5). We advocate clinical use of the Tono-Pen not only because of its unique miniaturization and ease in use, but because of the close correspondence with the manometrically measured intraocular pressure.

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EDITORIAL

The Leslie Dana Gold Medal

Robert C. Drews

In 1925, Mr. Leslie Dana, a prominent St. Louis businessman, established a trust fund to employ an artist and have dies made to strike a gold medal "to be known as the Leslie Dana Medal for the Prevention of Blindness."

Leslie Dana was born in St. Louis on Jan. 1, 1873. He graduated from the Massachusetts Institute of Technology and served in the Spanish American War. He was a patron of the arts and literature. In 1921, Mr. Dana was appointed to the Missouri Commission for the Blind. Much of the impetus to establish this state agency arose from the vigorous efforts of a St. Louis philanthropic organization, the Missouri Association for the Blind. Their mission, as well as that of the Missouri Commission, extended not only to welfare and social work among the blind, but to a strong program to prevent blindness as well. During his four years on the commission, Mr. Dana was devoted to the problems of the blind. He soon realized, however, the great importance of the prevention of blindness. The medal was established to spur this interest and to recognize distinguished service in the prevention of blindness.

Twenty-five years after the medal was first awarded, Mr. Dana was honored at a ceremony in his home by the National Society for the Prevention of Blindness with a special merit medal and an honorary lifetime membership certificate.

The original trust document stipulated that "so far as practicable its award shall be made annually in the City of St. Louis," and that the recipient should be provided with the opportunity to make an address to the Association "and allied organizations" on a topic related to "Conservation of Eyesight."

The officers and directors of the Missouri Association of the Blind were appointed trustees for the fund. Nominations could be made by any organization or individual interested in the conservation of vision, but selection of the recipient was made by the New York National Committee for the Prevention of Blindness and approved by the Board of Trustees of the Fund.

The Missouri Association for the Blind be-

came the St. Louis Society for the Blind and the National Committee for the Prevention of Blindness became the National Society for the Prevention of Blindness. In 1937, responsibility for the selection of the medal recipient was transferred to the Association for Research in Ophthalmology with approval of the National Society for the Prevention of Blindness and the St. Louis Society for the Blind. Subsequently, the selection reverted again to the National Society for the Prevention of Blindness. In 1962, the medal was temporarily discontinued when the rising price of gold and the cost of ceremonies outside of St. Louis greatly exceeded the yield of the trust. After consultation with Mrs. Dana, the fund was transferred to the St. Louis Eye Bank for use in blindness prevention. In 1970, with the approval of Mr. Dana's children, the St. Louis Society for the Blind reinstituted the medal, adhering to the original trust document concerning the criteria for selection of the recipient and the location of the award ceremony in St. Louis.

Over the years the Dana Gold Medal has become one of the most prestigious awards in the field. The medal itself (Figure) was designed and modeled by the sculptor Christian Peterson of Boston and executed by the J. Bolland Jewelry Company. Although of the European School, Peterson is best known for his life-size busts of New England governors and Boston notables, and for the designs he created for many national historic events.



Figure (Drews). The Leslie Dana Gold Medal.

Great care has been taken in the selection of the medal recipients. Indeed, they constitute a "Who's who" in this field (Table), a list to which all recipients have felt honored to belong. The Leslie Dana Gold Medal has been awarded to an international group, and its recipients include physicians, educators, welfare administrators, social workers, and organizers of welfare associations.

The first recipient was Edward Jackson. The presentation to Dr. Jackson was made by Mr. Lewis H. Carris, Managing Director for the National Society for the Prevention of Blindness. Apparently Edward Jackson's last official act was to present the Leslie Dana Medal to Mr. Carris himself, in 1942, two weeks before Dr. Jackson's sudden death.

The criteria for the selection of the medal recipient in the original trust document were as follows:

1. Long meritorious service for the conservation of vision and the prevention and cure of diseases dangerous to eyesight.
2. Research and instructions in ophthalmology and allied subjects.
3. Social service for the control of eye diseases.
4. Special discoveries in the domain of general science or medicine of exceptional importance in conservation of vision.

Social work in care for blind people and the problems of blindness was also quickly added to this list as a worthy criterion for the award of the medal. In 1926, the second medal was awarded to Miss Louisa Lee Schulyer, who had founded the New York State Charities Aid Association in 1872. She later founded the New York State Committee for the Prevention of Blindness and was a member of the Executive Committee of the National Society for the Prevention of Blindness.

The next medal will be awarded June 24, 1988, to Research to Prevent Blindness, through its president, Mr. David Weeks. This is the first time that the award of the medal recognizes an organization that has been outstanding in the field of prevention of blindness.

The work of those who have received the Leslie Dana Gold Medal reflects a monumental accomplishment in services to the blind and in the prevention of blindness.

Reprint requests to Robert C. Drews, M.D., 211 Meramec Ave., Clayton, MO 63105.

TABLE
PAST RECIPIENTS OF THE LESLIE DANA GOLD MEDAL

1925	Dr. Edward Jackson, Denver, Colorado
1926	Louisa Lee Schuyler, New York, New York
1927	Dr. Lucien Howe, Buffalo, New York
1928	Dr. Park Lewis, Buffalo, New York
1929	Prof. Ernst Fuchs, Vienna, Austria
1930	Dr. George E. deSchweinitz, Philadelphia, Pennsylvania
1931	Edward M. Van Cleve, New York, New York
1933	Dr. William H. Luedde, St. Louis, Missouri
1934	Dr. F. deLapersonne, Paris, France
1935	Dr. William H. Wilder, Chicago, Illinois
1936	Dr. John M. Wheeler, New York, New York
1937	Mrs. Winifred Hathaway, New York, New York
1938	Dr. Ellice M. Alger, New York, New York
1939	Dr. Edward C. Ellett, Memphis, Tennessee
1940	John M. Glenn, New York, New York
1941	Dr. Arnold Knapp, New York, New York
1942	Lewis H. Carris, New York, New York
1943	Dr. Walter B. Lancaster, Boston, Massachusetts
1944	Miss Linda Neville, Lexington, Kentucky
1945	Dr. William Zentmayer, Philadelphia, Pennsylvania
1946	Dr. Harry S. Gradle, Sherman Oaks, California
1947	Dr. Frederick H. Verhoeff, Boston, Massachusetts
1948	Dr. Lawrence T. Post, St. Louis, Missouri
1949	Dr. Conrad Berens, New York, New York
1950	Dr. William L. Benedict, Rochester, Minnesota
1951	Dr. E. V. L. Brown, Chicago, Illinois
1952	Miss Grace S. Harper, New York, New York
1953	Mrs. Harry S. Gradle (Audrey Hayden)
1954	Col. E. A. Baker, Toronto, Canada
1955	Mrs. Helenor Wilder Forerster, San Francisco, California
1957	Dual award to Miss Evelyn M. Carpenter, Monkton, Maryland, and Mrs. Eleanor Brown Merrill, Baltimore, Maryland
1958	Robert F. Irwin, Jr., Philadelphia, Pennsylvania
1959	Dr. Derrick T. Vail, Chicago, Illinois
1960	Dr. Frederick C. Cordes, San Francisco, California
1961	Dr. Everett L. Goar, Houston, Texas
1971	The Rev. Thomas J. Carroll L.L.D., Newton, Massachusetts
1973	Dr. C. Wilbur Rucker, Rochester, Minnesota
1975	Dual award to Sir John Wilson, C.B.E., and Lady Jean Wilson, Haywards Heath, England
1976	Dr. Thaddeus S. Szewczyk, Belleville, Illinois
1977	Dr. Bernard Becker, St. Louis, Missouri
1978	Dr. Peter C. Kronfeld, Tucson, Arizona
1980	Dr. Jules Stein, Los Angeles, California
1981	Dr. A. Edward Maumenee, Baltimore, Maryland
1982	Dr. Lorenz E. Zimmerman Washington, D.C.
1985	Dr. Frank W. Newell, Chicago, Illinois
1986	Dr. Marshall Parks, Washington, D.C.
1988	Research to Prevent Blindness, New York, New York

LETTERS TO THE JOURNAL

An Affinity Membrane Test for Superficial Corneal Herpes

Bryan M. Gebhardt, Ph.D., James Reidy, M.D., and Herbert E. Kaufman, M.D.

Lions Eye Research Laboratories, LSU Eye Center, Louisiana State University Medical Center School of Medicine. This study was supported in part by Public Health Service grants EY03150 and EY02672 from the National Eye Institute.

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We developed and tested an affinity membrane test for confirming the presence of herpesvirus in superficial corneal lesions. A protein-binding affinity membrane, used as a blotter, is gently touched to the corneal lesion. The membrane is permitted to dry for five minutes, and is then immersed in a 0.5% casein-blocking buffer containing a 1:1,000 dilution of horseradish peroxidase-conjugated anti-herpes simplex virus antibody for 15 minutes at room temperature. The membrane is washed in three changes of a 0.1% solution of Triton X 100 detergent in phosphate-buffered saline and two changes of deionized water and then immersed in a substrate solution made as follows: 100 mg of tetramethylbenzidine dissolved in 10 ml of dimethyl sulfoxide, and 1 ml of the tetramethylbenzidine solution diluted in 100 ml of 0.1 M sodium acetate/citrate buffer at pH 6.0 and 0.1 ml of 30% hydrogen peroxide.

Membranes that have adsorbed herpesvirus antigen from contact with an infected cornea develop a pattern of intense deep blue staining almost immediately upon contact with the tetramethylbenzidine solution. The reaction is complete within three to five minutes. Membranes without antigen and those blotted on nonherpetic corneal lesions remain colorless. The total time needed to obtain the results of this test is about 30 minutes.

This test for herpesvirus is simple, rapid, and extremely sensitive. Side-by-side comparisons of the immunoaffinity membrane test and the enzyme-linked immunosorbent assay using laboratory grown viral antigen indicate that the test is at least as sensitive as the enzyme-linked immunosorbent assay procedure.

We used the affinity membrane test in a large number of control (uninfected) and herpesvirus-infected rabbit corneas. In more than 20 control samples and more than 40 herpes-infected samples, no cross reactions or false-positive results were found.

The affinity membrane technique acts as a replica blotter in that the herpes simplex virus type 1 lesion on the cornea, whether it is a dendrite, a punctate epithelial lesion, or a geographic ulcer, is duplicated exactly on the membrane in the form of an immunospecifically stained area (Figure). This confirmatory test, which was developed in the rabbit eye, has immediate application to the diagnosis of lesions in the human cornea caused by virtually any infectious agent for which enzyme-labeled antibodies are available. Thus, the diagnosis of adenovirus and *Chlamydia* may be easily accomplished by using simple modifications of this approach.

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Letters must be typewritten, double-spaced, on 8 1/2 x 11-inch bond paper with 1 1/2-inch margins on all four sides. (See Instructions to Authors.) They should not exceed 500 words of text. A maximum of two black-and-white figures may be used; they should be cropped to a width of 3 inches (one column). Color figures cannot be used. References should be limited to five.

Letters may be referred to outside editorial referees for evaluation or may be reviewed by members of the Editorial Board. All letters are published promptly after acceptance. Authors do not receive galley proofs but if the editorial changes are extensive, the corrected typescript is submitted to them for approval.

These instructions markedly limit the opportunity for an extended discussion or review. Therefore, THE JOURNAL does not publish correspondence concerning previously published letters.

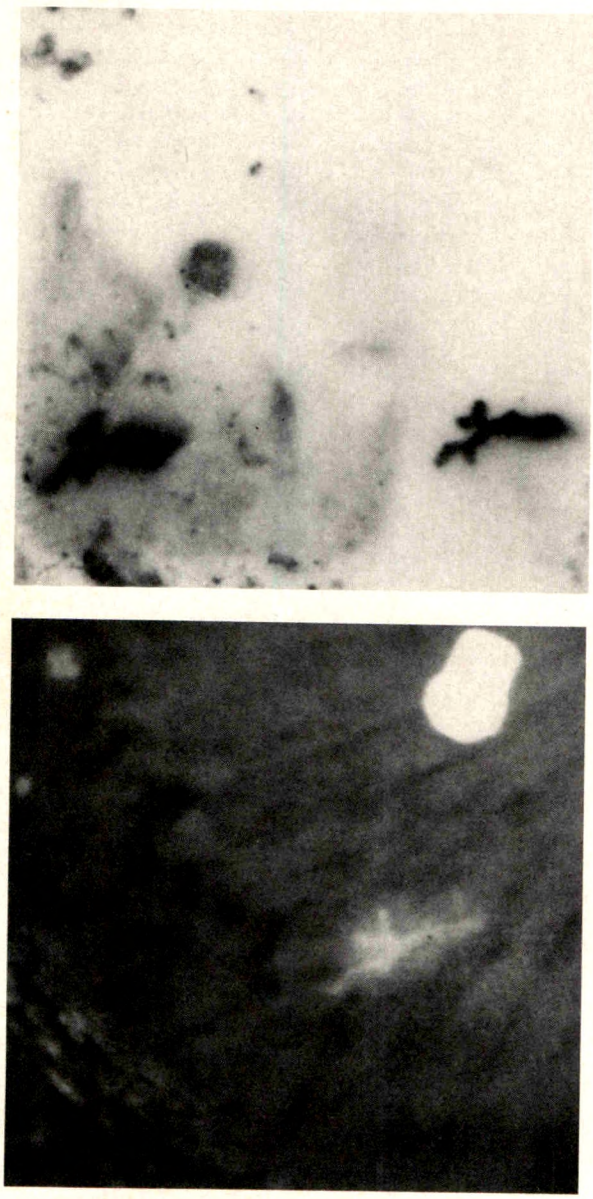


Figure (Gebhardt, Reidy, and Kaufman). Typical example of positive affinity membrane test and the herpes simplex virus-infected cornea on which the membrane was blotted. Top, Membrane exhibiting two replicas of a corneal epithelial dendrite obtained by touching the dendrite two times in succession. The membrane was treated as described in the text and the deep blue color developed, indicating the presence of herpes simplex virus antigens in the dendrite. Bottom, Slit-lamp photomicrograph of corneal epithelial dendrite from which the affinity membrane test shown above was developed. The epithelial lesion and the blue pattern on the affinity membrane are replicas of each other.

Topical Timolol-Induced Arthropathy

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The possible association between arthropathies and systemic beta-blockers dates back to 1976 when Fraser and Irvine[1] reported a case of knee pain induced by practolol. The knee pain subsided when practolol was discontinued, but reappeared when the medication was reintroduced. Polyarthritis has been described in association with propranolol hydrochloride and oxprenolol hydrochloride.[2,3]

Similarly, acute psoriatic arthropathies that were caused by oxprenolol hydrochloride have resolved without recurrence after drug withdrawal. Furthermore, beta-blocker-induced development of an illness resembling idiopathic systemic lupus erythematosus has been reported.[4] Although several articles have called attention to the number of cases of arthralgia associated with systemic, adrenergic beta-blockers, there is currently no controlled study in the literature. Manifestations of beta-blocker-induced arthralgia range from a multisystem immunologic syndrome to less serious, isolated arthropathies.

A 61-year-old woman had been taking timolol 0.25% twice daily in both eyes for presumed ocular hypertension. Her systemic history included recent onset of mild arthralgias in both knees for which she took naproxen. On initial ocular examination, her intraocular pressure was 23 mm Hg in the right eye and 28 mm Hg in the left eye. Although results of visual field testing were normal, the optic nerve heads showed glaucomatous change. The concentration of timolol was increased to 0.5%.

Several months later, the patient complained of sharp, constant pains in her knees. There were no other arthritic complaints. She was taught nasolacrimal occlusion and continued taking the timolol. One month later, the knee pains had decreased but she was still uncomfortable. Her orthopedic surgeon was considering bilateral knee surgery. Timolol was discontinued and the patient was treated with dipivefrin. Her intraocular pressure remained controlled. Over the next month, her knee pains resolved completely; she discontinued using the knee braces, and she walked without a handicap. There has been no recurrence of

joint pains of any sort over the subsequent 14 months.

Because significant blood levels of beta-blockers can be achieved by topical administration,[5] physicians should be aware of possible joint-related problems when topical beta-blocker therapy is used for the treatment of glaucoma.

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Nitrous Oxide Warning

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Nitrous oxide is frequently used in ophthalmologists' offices for treatment of trichiasis, benign skin lesions, cyclocryotherapy, and simple cryopexy. The following is a case report that was submitted to the National Registry of Drug-Induced Ocular Side Effects, in which nitrous oxide asphyxiation resulted in the death of a part-time employee in an ophthalmologist's office.

A 17-year-old boy frequently worked alone after hours as a computer programmer in an ophthalmologist's office. He was found dead, with a plastic bag over his head, and with his hands closing the bag around his neck. No evidence of foul play, suicide, or drugs was found. One of the boy's friends stated to the police that his friend had spoken of "putting gas in a bag and breathing it to get high sometimes while he was at work." A canister of nitrous oxide was found on a cryo cart in the area of the office that was used for minor surgery. The boy's fingerprints on the canister suggested that accidental nitrous oxide asphyxiation was the cause of death. This was later confirmed.

Commonly known as "laughing gas," nitrous oxide results in euphoria and numbness when inhaled, and is often used as an anesthetic in medical offices. In ophthalmologists' offices, however, nitrous oxide is used as a cryogen and not as a drug. Therefore, it is not set up for mask usage. To obtain high respiratory concentrations of nitrous oxide without a mask would require tubing or a bag as described. Ophthalmologists may consider storing this agent when it is not being used in a locked cabinet.

Retinal Artery Occlusion Associated With Tranexamic Acid Therapy

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Tranexamic acid is an antifibrinolytic agent currently under investigation by the Food and Drug Administration. It is both a competitive inhibitor of plasminogen activation and a noncompetitive inhibitor of plasmin, similar in action to aminocaproic acid. The antifibrinolytic activity increases thrombotic tendency and decreases risk of hemorrhage.[1] Tranexamic acid has been used to treat uterine bleeding,[2] uncontrolled gastrointestinal bleeding,[3] and acquired C1 esterase inhibitor deficiency-induced angioedema.[1] It is also used to treat traumatic hyphemas as an alternative to aminocaproic acid.

Reported complications of tranexamic acid show an increase in thrombotic proclivity, and include one case of mesenteric venous throm-

bosis[1] and four cases of intracranial thrombosis with two deaths.[2,4] The incidence of complications is low. We encountered a case of a branch retinal artery occlusion in a patient treated with tranexamic acid for hemorrhagic cystitis.

Acute myelogenous leukemia was diagnosed in a 57-year-old woman. After consolidation chemotherapy failed on three occasions, she underwent an autologous bone marrow transplantation. She received two three-day courses of aminocaproic acid (500 mg intravenously, twice daily) for cyclophosphamide-induced hemorrhagic cystitis, but did not tolerate the medication. Ten days later, tranexamic acid was administered (750 mg intravenously, twice daily) for persistent hemorrhage. On the fifth day of therapy, the patient reported blurry vision. Bedside examination documented visual acuity of Jaeger 1 in both eyes. Results of Amsler grid testing showed a scotoma above fixation in the right eye. Ophthalmoscopy of the right eye disclosed a tertiary branch retinal artery occlusion, located between the inferior temporal arcade and the fovea. The platelet count was 62,000/mm^3. Results of prothrombin time and partial thromboplastin time were normal.

The tranexamic acid was suspected as the inciting factor leading to the arterial occlusion and was discontinued. No other thrombotic episodes were observed.

Although tranexamic acid cannot absolutely be implicated in this case of branch retinal artery occlusion, we believe that ophthalmologists should be aware of potentially serious thrombotic side effects of the medication.

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Microinfusion of Thrombin Solution in Vitreous Surgery

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Thompson and coworkers[1] described the use of an intraocular infusion of bovine thrombin to reduce bleeding during vitreous surgery. They added thrombin to the infusion bottle in a concentration of 100 mg/ml. Of their patients, 20% developed severe inflammatory reactions postoperatively. The incidence of inflammation was decreased, however, when the vitreous cavity was irrigated at the end of surgery with fluid that did not contain thrombin.

M. B. Landers, M.D. (oral communication, 1986) suggested that a 100-mg/ml thrombin solution be infused with a syringe that is linked to the intraocular infusion line with a three-way stopcock. When hemorrhage occurs, the stopcock is opened and the thrombin-containing solution is infused. Because the thrombin solution is used only when hemorrhage occurs, the incidence of inflammation may be decreased.

At my institution, we have been using a method for the delivery of thrombin that decreases further the quantity of thrombin infused into the eye, while retaining its effectiveness. When vitreous surgery is performed for the complications of diabetic retinopathy, a tissue manipulator* is used frequently. This instrument combines a fiberoptic light source with a cautery tip, which has a 30-gauge end-opening port that can be used as suction forceps (Figure). The suction is applied with a syringe controlled by an assistant. Although the syringe is usually filled with the same solution used for intraocular infusion, in this method the syringe is filled with a 100-mg/ml solution of thrombin that has been mixed in BSS Plus. When hemorrhage is encountered, the thrombin solution can be used to irrigate blood away from the site and aid in hemostasis. The tip of the manipulator can then be used to

*The Grieshaber tissue manipulator was designed by Brooks W. McCuen II, M.D., and Dyson Hickingbotham of Duke University Eye Center.

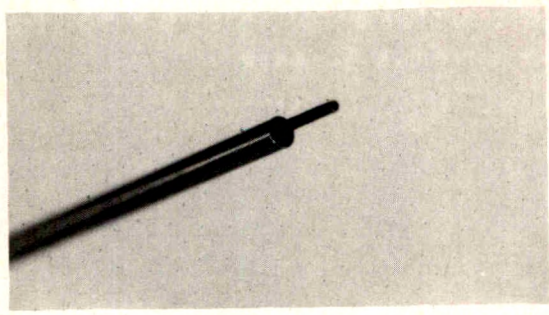


Figure (Cowan). The tip of the instrument, with the 30-gauge cautery tip and suction port extending past the fiberoptic bundle.

cauterize the bleeding site. This method limits the total amount of infused thrombin to the amount delivered directly to the source of the hemorrhage. I believe that this method decreases the incidence and severity of inflammatory reactions even further. To prevent blockage of the suction/infusion line by material precipitated from the thrombin solution, one must be careful to clean the line thoroughly after use.

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Low-Dose Fluorescein Angiography

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Fluorescein angiography uses the fluorescence characteristics of a vegetable dye, sodium fluorescein, to assess abnormalities in the choroid, retina, optic nerve, and iris. Wessing[1] studied the proper dose and concentration of the dye when the technique was first introduced, and since that time it has been customary to use no less than 5 ml of 10% dye.

We evaluated a 2-ml injection of 10% solution in 500 consecutive cases that included a wide variety of disorders involving the retina, choroid, and optic nerve head. Fifty patients had media opacities and nine patients had small pupils (<3 mm).

The fluorescein dye was injected in the antecubital vein as quickly as possible, and photographs were taken using a Zeiss fundus camera with the flash power set at 200 to 240 Wsec throughout the transit. We used Kodak 400 ISO T-Max professional film and push-processed it with Kodak developer D11 straight for 7.5 minutes at 68 F. Kodak rapid fixer was used for seven minutes at 68 F. Contact sheet transparencies were obtained with a printing time approximately 30% shorter than that of the 5-ml dose.

The fluorescein angiograms were reviewed by four experienced observers. It was the reviewers' impression that details important for diagnosis were not lost by using the lower dose. Because less fluorescein was used, the transit time was shortened, and photographs taken at five minutes provided as much information as those taken at more than 15 minutes with a 5-ml dose, thus decreasing the waiting time for the photographer and patient. Most importantly, patients tolerated the 2-ml injection better, with fewer instances of nausea and vomiting. Finally, costs were reduced by using less dye.

We believe that advances in film and developer chemistry have made possible the use of low-doses of fluorescein for angiography. The Kodak T-Max film uses tabular grain technology that produces high-contrast pictures and responds well to push processing. Contrast is enhanced further by using a developer with high hydroquinone content and a high pH (Kodak D11 developer). This all helps compensate for any decreased fluorescence caused by using a lower dose injection.

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Inflammatory Glaucoma Associated With Sweet's Syndrome

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I examined a 58-year-old man because of fever, decreased vision, photophobia, bilateral chemosis, and increased intraocular pressure for two days. Idiopathic thrombocytopenic purpura had been diagnosed almost ten years previously and the patient had subsequently required a splenectomy. Sweet's syndrome (acute febrile neurotrophilic dermatosis)[1-3] had been diagnosed at age 54 years based on results of a facial skin biopsy and the patient's clinical history of recurrent episodes of fever, arthralgia, and painful erythematous plaques on the face. The patient had a history of corticosteroid-dependent emphysema and microscopic hematuria. His medications included prednisone and colchicine. He denied any current use of ocular medications.

Over the preceding nine months, the patient had had four episodes of bilateral ocular inflammation associated with fever, facial swelling, decreased vision, photophobia, pain, and markedly increased intraocular pressure. During the first episode of inflammation, bilateral argon laser iridotomy and trabeculoplasty had been performed without significantly lowering the intraocular pressure. Previous medical treatment consisting of pilocarpine, dipivefrin, and levobunolol also failed to reduce the pressure. Between bouts of inflammation, his eyes were quiet, with a visual acuity of 20/20 and normal pressure.

At the initial examination, visual acuity was counting fingers in both eyes. His neck and lower face were mildly swollen. External examination disclosed mild eyelid swelling, chemosis, mild corneal epithelial and stromal edema, several keratic precipitates, moderate (+2) anterior chamber cell and flare, and patent iridotomy in both eyes (Figure). Intraocular pressure was 30 mm Hg in both eyes. Gonioscopy showed open angles to the ciliary body band bilaterally. Ophthalmoscopy could not be performed because of the hazy media. B-scan ultrasonography demonstrated a clear vitreous with questionable thickening of the choroid.

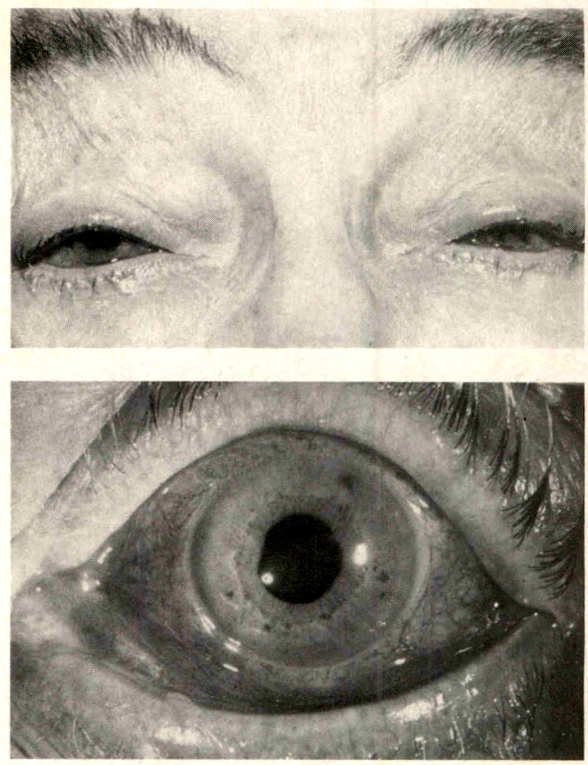


Figure (Fourman). Top, Mild bilateral eyelid swelling and chemosis noted on initial examination. Bottom, Left eye has chemosis, diffuse episcleral and scleral injection, and mild corneal haziness caused by edema.

Computed tomography was not performed because of an allergy to intravenous dye.

A diagnosis of anterior uveitis with increased intraocular pressure (inflammatory glaucoma) was made. The patient was then treated with 60 mg of prednisone daily, 250 mg of acetazolamide four times a day, dexamethasone 0.1% drops hourly in both eyes, and homatropine 2% drops three times a day in both eyes.

Within four days, the patient's symptoms had resolved. Visual acuity improved to 20/30 in both eyes. The eyelid swelling, chemosis and corneal edema, and intraocular inflammation were almost gone. Intraocular pressure was 16 mm Hg bilaterally. Ophthalmoscopy showed normal optic nerves and vasculature. There were no vitreous cells, retinal infiltrates, or choroidal folds. Medications were tapered over the ensuing three weeks without recurrence of the symptoms. Six months later, the patient was taking his usual oral medications without relapse or need for ocular therapy.

Sweet's syndrome is a rare but distinctive dermatologic disorder. Although the pathogenesis is unknown, a type III hypersensitivity reaction to an as yet unknown antigen has been postulated.[1] It is characterized by the abrupt appearance of painful, erythematous cutaneous nodules and plaques on the arms, face, or neck; fever; arthralgia; ocular inflammation; leukocytosis; and increased erythrocyte sedimentation rate. Associated infections or underlying malignancy, especially leukemia, may be present. Histologic examination shows neutrophilic infiltration in the dermis without vasculitis. Ocular involvement, described as either a conjunctivitis or episcleritis, has been reported to occur in 4% to 72%[2] of patients, although no detailed ophthalmologic examination has been noted.

This patient with Sweet's syndrome and ocular involvement not only had chemosis, but also had an associated anterior uveitis with increased intraocular pressure. Episcleritis or mild scleritis may have also been present given the history of pain. Results of computed tomography may have aided in diagnosing posterior scleritis but could not be performed in this patient. In contrast to other reports describing the involvement as benign, the increased intraocular pressure presents a vision-threatening complication.

Corticosteroid therapy appears to resolve rapidly the dermatologic and ophthalmologic manifestations of this disorder. Recurrences are common, especially in patients with an associated leukemia or during the tapering of corticosteroid therapy. Chronic corticosteroid therapy may be required. Other forms of therapy, such as colchicine and potassium iodide, have been used to treat the skin involvement, but their effects on the ocular manifestations are unknown.[1]

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Pupillary Dilation in Eyes With Pseudoexfoliation Syndrome

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Pseudoexfoliation has recently been implicated as an important risk factor for vitreous loss in cataract surgery.[1-3] This is attributed to increased zonular fragility with consequent rupture.

A clinical observation prompts me to emphasize the role of inadequate pupillary dilation in the association of pseudoexfoliation and zonular rupture or vitreous loss. I observed that many eyes with clinically apparent pseudoexfoliation often withstood the usual manipulation of the nucleus during phacoemulsification as well as nonpseudoexfoliation eyes. However, pupillary dilation in eyes with pseudoexfoliation was often less than normal, a finding that has been previously reported.[3] I undertook a brief study to measure the amount of pupillary dilation in eyes with pseudoexfoliation relative to normal, as I could find no data regarding this in the literature.

Pupillary dilation was measured in 17 patients with clinically apparent pseudoexfoliation syndrome[4] in one eye only. The amount of dilation was measured with a pupillometer one-half hour after instillation of one drop each of tropicamide 1% and phenylephrine hydrochloride 2½%. Pupil diameters were measured before viewing the anterior segment with the slit lamp. None of these patients had ever been treated with pilocarpine eyedrops. In 16 of the 17 patients, there was less dilation of the eyes with pseudoexfoliation, and in only one patient was the dilation equivalent (Table). Compared to fellow eyes or an age- and sex-matched population, the difference was statistically significant ($P < .001$). When calculating dilation as a percentage of theoretically visible maximum dilation (10 mm), or pupillary area, the differences are notable. Increasing the dilation of the pupil, for example, from 5.5 to 7.0 mm results in an almost 60% greater pupillary area. The dilating regimen may have been submaximal, but even with stronger mydriatics, relative differences should be maintained. Although this was not a masked study and bias was thus not totally eliminated, slight differences in abso-

TABLE
PUPILLARY DIAMETER MEASUREMENTS IN PATIENTS WITH MONOCULAR PSEUDOEXFOLIATION SYNDROME*

PATIENT NO., AGE (YRS), SEX	PUPIL SIZE (MM) R.E.	L.E.
1, 74, F	6.0†	8.0
2, 62, F	6.0†	8.5
3, 74, M	5.5†	6.0
4, 56, F	8.5	6.5†
5, 54, F	7.0†	8.5
6, 72, F	7.0	5.5†
7, 79, F	7.0	5.5†
8, 75, F	7.0	5.0†
9, 75, M	7.0†	7.5
10, 66, F	7.0†	9.0
11, 69, F	5.0†	6.5
12, 75, F	8.0	8.0†
13, 66, F	7.0	6.0†
14, 77, F	5.5†	8.0
15, 70, F	9.0	7.0†
16, 52, F	8.0	6.0†
17, 66, M	7.0†	8.0

*Differences between pseudoexfoliation and fellow eyes or an age- and sex-matched normal population were significant at $P < .001$.

†Denotes eye with pseudoexfoliation.

lute dilation measurements might have occurred, but the differences between normal eyes and eyes with pseudoexfoliation syndrome were clearly evident. If one considers a 1-mm difference as unmistakable, the data show 14 of the 17 eyes in the pseudoexfoliation group had a difference of ≥1 mm, whereas none of an age- and sex-matched normal group showed this phenomenon.

Although there is clinical and histopathologic evidence of abnormalities of iris structure in the pseudoexfoliation syndrome,[4,5] to the best of my knowledge, measurement of pupil dilation in pseudoexfoliation syndrome has never been studied. In the detailed analysis of risk factors in cataract surgery by Guzek and colleagues,[1] pupillary size was clearly determined to be the most significant risk factor for vitreous loss. In that same study, pseudoexfoliation syndrome was also confirmed to be a risk factor, but pupillary dilation and pseudoexfoliation were not specifically related. My data indicate that the pupil in pseudoexfoliation generally dilates submaximally. This is presumably related to iris infiltration and fibrosis from the pseudoexfoliation.[5]

This finding has clinical relevance as the increased incidence of zonular rupture or vitreous loss during cataract surgery in eyes with pseudoexfoliation often may be caused by a relative increase in pressure required to deliver a large nucleus through only a moderately dilated pupil. This is consistent with the data of Guzek and associates.[1] Inadequate dilation as a risk factor has been previously noted by Tarkkanen.[3] The pupils with pseudoexfoliation syndrome may dilate moderately, which may be misleading to the surgeon who expects a routine experience during cataract surgery. In a glaucoma patient who has been on long-term miotic therapy and who dilates poorly, the surgeon expects routinely to deal with this by sphincterotomies or sector iridectomy. Moderate dilation of pupils with pseudoexfoliation may not trigger the same thinking and may lead to unexpected problems with nucleus delivery on the basis of pupillary restriction, or perhaps inadequate anterior capsulotomy resulting from this. Although zonular fragility may be the major cause of the increase in zonular rupture or vitreous loss with extracapsular cataract surgery in pseudoexfoliation syndrome, the resistance of a poorly dilated fibrotic iris plays a role. Certainly faced with zonular fragility, one wants to minimize pressure on the globe during nucleus delivery. One should vigorously attempt to dilate the pupil maximally preoperatively. Surgeons should consider surgical measures to alter pupil size in a patient with pseudoexfoliation and only moderate dilation (≤6 mm) about to undergo cataract surgery.

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Scleromalacia Associated With Vogt-Koyanagi-Harada Syndrome

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Vogt-Koyanagi-Harada syndrome is a chronic disorder characterized by bilateral progressive panuveitis affecting the choroid, ciliary body, and iris.[1-5] The disease is regarded as an autoimmune attack directed against melanin-bearing cells.[1,3] Vogt-Koyanagi-Harada syndrome affects various organs containing melanocytes and may be associated with acoustic disturbances, meningitis, hair loss, and vitiligo. Although the sclera may contain melanocytes at the site of emergence of long ciliary nerves, scleral involvement is rare. I examined a patient with Vogt-Koyanagi-Harada syndrome who developed focal scleritis at the site of emergence of long ciliary nerves in the areas of melanocytic aggregates anterior to the insertion of the recti muscles in both eyes. The patient later developed evidence of scleromalacia.

A 21-year-old woman had a history of recurrent episodes of redness of both eyes and blurring of vision for two years. She had been given oral and topical corticosteroids by another physician and had also previously undergone bilateral cataract extraction. She reported a history of dysacousia and hair loss.

On examination visual acuity was R.E.: 20/80 and L.E.: 20/200 with aphakic correction. Intraocular pressure by applanation tonometry was R.E.: 16 mm Hg and L.E.: 15 mm Hg. Vitiligo of the eyelids and poliosis of the eyelashes in both eyes were noted. The right eye showed areas of focal scleritis anterior to the insertions of the recti muscles and areas of scleral thinning superiorly and temporally (Fig. 1). The anterior chamber was deep. The anterior chamber reaction showed 2+ flare and 2+ cells in the right eye. Small to medium sized keratic precipitates

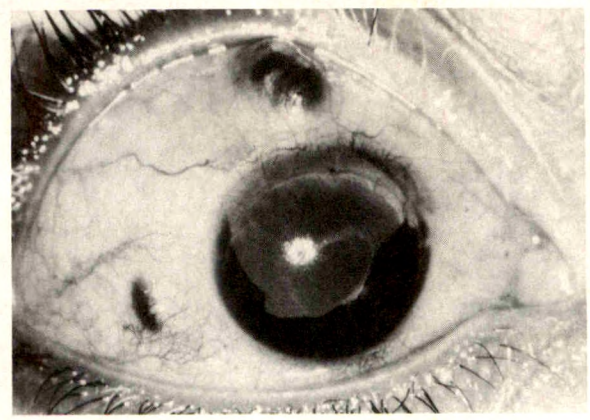


Fig. 1 (Tabbara). Note areas of focal scleritis with scleral thinning anterior to the insertion of the recti muscles.

were also present. The pupil had a sector iridectomy superiorly. Ophthalmoscopy of the right eye showed peripapillary edema with multifocal choroiditis, retinal pigment epithelial atrophy, and mottled scars in the fundus. The left eye showed evidence of scleromalacia superiorly with anterior staphyloma (Fig. 2). Focal areas of scleritis with scleral thinning temporally and inferiorly were also noted anterior to the insertion of the lateral and inferior recti muscles, respectively. The left eye showed 1+ flare and 1+ cells with small keratic precipitates over the endothelium. Ophthalmoscopy of the left eye demonstrated loss of pigment in the retinal pigment epithelium and multiple focal areas of choroidal scars and peripapillary atrophy.

Systemic and complete medical examinations showed no evidence of other autoimmune diseases.

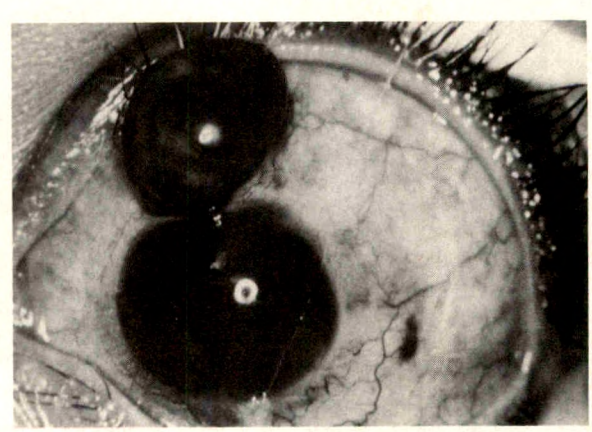


Fig. 2 (Tabbara). Scleromalacia superiorly with anterior staphyloma in a patient with Vogt-Koyanagi-Harada syndrome.

Scleritis is not commonly encountered in Vogt-Koyanagi-Harada syndrome since the disease is caused by an autoimmune attack directed against melanin-bearing cells. Meningeal signs and symptoms represent an inflammatory process in the meninges because of the presence of residual melanocytes derived from the neural crest. The sclera may contain melanocytes, especially at the site of exit of the long ciliary nerves anterior to the recti muscles. The autoimmune attack on melanocytes in the sclera may lead to focal scleritis and may cause the destruction of the collagen fibers.

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Safety and Effectiveness of Magnetic Resonance Imaging of Choroidal Melanoma Patients With Episcleral Tantalum Rings After Proton Beam Irradiation

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During the last 12 years approximately 1,200 patients with choroidal melanomas have been treated with proton beam irradiation at the Harvard Cyclotron. Before irradiation treatment, the patients are admitted to the Massachusetts Eye and Ear Infirmary for the suturing of four 2.5-mm diameter tantalum rings, which serve as reference markers for radiographic alignment of the tumor with the proton beam.[1] These rings remain permanently sutured on the sclera.

Recently, concern has been expressed as to whether magnetic resonance imaging can be performed safely and effectively after proton beam irradiation on choroidal melanoma patients with episcleral tantalum rings. Magnetic resonance imaging is now being used to assess the location and size of choroidal melanomas, and is likely to be used more in the future. Magnetic resonance is known to be a safe, noninvasive technique with many medical applications; potential hazards have so far only been known to exist for the imaging of subjects with ferromagnetic foreign bodies or cardiac pacemakers.[2,3] Hazards associated with tantalum rings may include spatial disruption of the rings caused by magnetic torque or heating of the rings induced by radiofrequency pulses. Effective magnetic resonance imaging depends on the absence of artifacts resulting from the rings. Such artifacts make the evaluation of these eyes with computed tomography difficult.

Pure tantalum is nonmagnetic and has been shown to have no torque in a clinical magnetic resonance imaging magnet.[4] We attempted to determine whether tantalum might experience an increase in temperature as the result of a series of radiofrequency pulses. A temperature change of a few degrees in the tantalum rings caused by the imaging process could cause injury to the eye. By using enucleated human eyes as subjects we also wanted to ascertain whether high quality images can be produced despite the presence of tantalum rings.

The temperature response of a tantalum ring to radiofrequency pulses was monitored by a microthermistor bead with a temperature coefficient of −3.9% C. The leads to the thermistor were tinned and soldered to two twisted insulated copper wires (26 G, 0.5 m long), which in turn were soldered to 10 m of stranded wire cable. The cable ends were connected to the junctions of a Wheatstone bridge with an elec-

tronic galvanometer used as a null detector. A temperature change of as little as 0.08 C was detectable and corresponded to one division on the meter. The tantalum ring was secured to the microthermistor bead with cement (Fig. 1), sealed, and mounted on a surface coil tuned to 81 MHz placed in the center of a 4.7-tesla, 30-cm bore magnet. Radiofrequency energy was applied in both the continuous wave and hard pulse modes, using the MIT-IBM imaging system.

Following an initial decrease in temperature caused by the coolness of the magnet bore, the system was allowed to equilibrate for ten minutes. Radiofrequency energy was then applied for five minutes at power levels ranging from 20% to 80%. No heating was observed. The only temperature change detected by the thermistor was a slight negative drift of 0.12 degree. Hard pulses were then applied for five minutes at 60% full power, with pulse width 100 μsec and recycle delay ranging from 1 to 0.5 second. Again, no heating was detected. Removing the tantalum ring from its adiabatic chamber in the magnet and exposing it to room air resulted in a temperature increase of 4.3 C. Thus, we confirmed that no detectable heating of tantalum is caused by radiofrequency energy and there is no risk to an eye bearing tantalum rings.

Effective magnetic resonance images have been obtained from enucleated human eyes bearing tantalum rings.[5] High quality T_1- and T_2-weighted proton magnetic resonance images were produced from such eyes; minor artifacts appear as bright rings directly beneath the tantalum rings (Fig. 2). All other tissues within the eye produced the expected magnetic resonance image properties. The clinician may therefore obtain magnetic resonance images of patients with episcleral tantalum rings with the confidence that the procedure is not hazardous because of magnetic torque or radiofrequency-induced heating, and that it can yield effective magnetic resonance images.

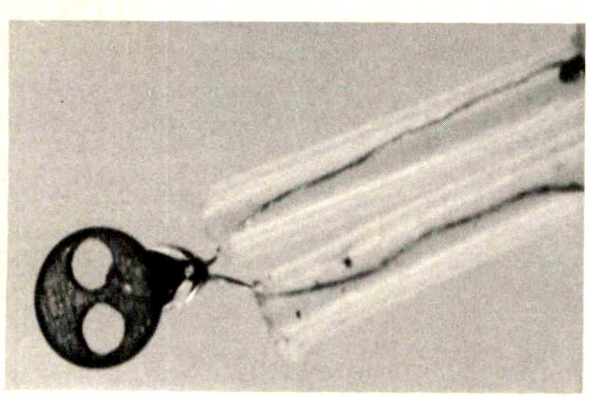


Fig. 1 (Smith and associates). Microthermistor bead mounted on tantalum ring.

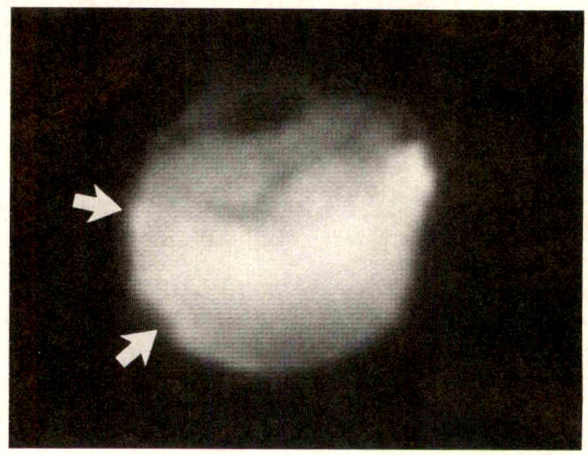


Fig. 2 (Smith and associates). T_1-weighted proton magnetic resonance image of enucleated human eye. Arrows indicate minor artifacts caused by tantalum rings.

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Orbital Pseudotumor in a Patient With AIDS

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Infection by human immunodeficiency virus (HIV) predisposes the AIDS patient to opportunistic infection by various pathogens. The association of AIDS with ocular involvement by numerous pathogens and neoplasms has been reported, including cytomegalovirus, Epstein-Barr virus, herpes simplex virus, varicella-zoster virus, HIV itself, poxvirus (causing molluscum contagiosum), *Toxoplasma gondii*, *Candida* species, *Cryptococcus neoformans*, *Mycobacterium tuberculosis*, *M. avium-intracellulare*, *Treponema pallidum*, *Pneumocystis carinii*, Kaposi's sarcoma, and Burkitt's lymphoma.[1-3]

A 22-year-old woman had a two-day history of severe, deep right-sided orbital pain, which was worse with ocular movement. The patient exhibited signs of acute orbital inflammation, including erythema, tenderness, and periocular and conjunctival edema. The patient also had numerous pearly, umbilicated periocular skin lesions typical of molluscum contagiosum. Computed tomography of the orbits disclosed an enhancing mass lesion in the region of the right lacrimal fossa, as well as adjacent soft tissue edema, scleral enhancement, and orbital infiltrates without sinus involvement or bony erosion (Figure). The patient was afebrile. Total white blood cell count was 5,000/mm^3 and there was no lymphocytosis.

The diagnosis of nonspecific orbital inflammatory syndrome was based on clinical and computed tomography findings. The patient's prompt and complete response to high-dose oral corticosteroids further confirmed the diagnosis. Four months after the initial manifestation the patient developed fevers, cough, and malaise. Positive HIV antibody titers and cytomegalovirus were cultured from a lung biopsy specimen. A history of sexual contact with an intravenous drug abuser was elicited. Three months later the patient developed numerous cotton-wool spots in the posterior fundus, suggestive of a bilateral ischemic process.

Orbital lymphoid lesions including reactive lymphoid hyperplasia and atypical lymphoid hyperplasia may be considered in the differential diagnosis of nonspecific orbital inflammation. Inflammatory pseudotumor differs from reactive lymphoid hyperplasia and atypical lymphoid hyperplasia both histologically and clinically. Inflammatory pseudotumor is a hypocellular lesion with a nonspecific infiltrate of inflammatory cells consisting of neutrophils, mature lymphocytes, plasma cells, and histiocytes in a variably dense fibrous stroma. Reactive lymphoid hyperplasia and atypical lymphoid hyperplasia are hypercellular lesions with sheets of mature lymphocytes, scattered plasma cells, and histiocytes devoid of a significant fibrous stroma.[4] Clinically, pseudotumor exhibits pain and erythema, with immediate and complete response to corticosteroid therapy. Reactive lymphoid hyperplasia and atypical lymphoid hyperplasia have a limited response to corticosteroids and are not commonly associated with pain and erythema.[5]

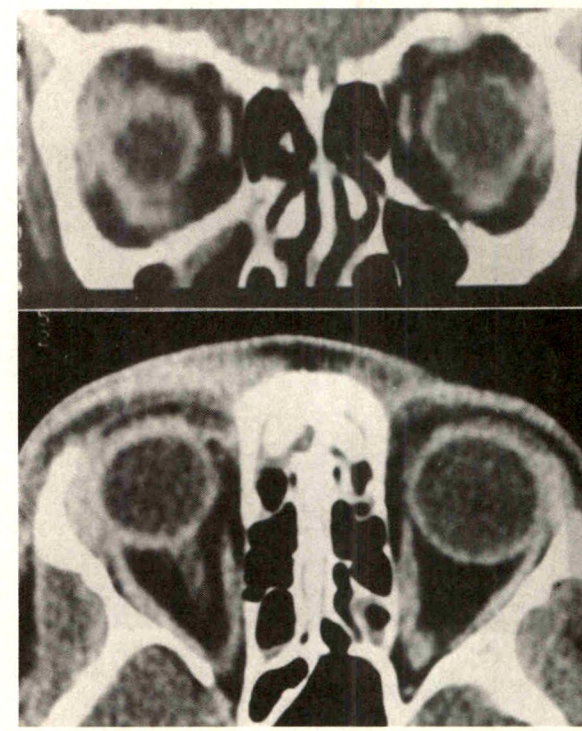


Figure (Benson, Linberg, and Weinstein). Computed tomography of the orbits showed enhancing mass lesion of the right lacrimal fossa with adjacent soft tissue edema, scleral enhancement, and orbital infiltrates. No sinus involvement or bony erosion present.

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Pasteurella multocida Meningitis Following Orbital Exenteration

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Pasteurella multocida, a commensal in the upper respiratory tract of mammals and birds, is a frequent cause of infection in animals.[1] Rarely, humans are infected from animal bites or close contact with household pets.[1,2] *Pasteurella multocida* meningitis has been reported after compound skull fractures, intracranial surgery, and ethmoid sinus surgery.[3] We encountered a case following orbital surgery.

Without prophylactic antibiotics, a 34-year-old man underwent exenteration of his right orbit for a long-standing, progressive orbital myxoid liposarcoma. The exenteration involved all soft tissues to the superior orbital fissure and optic canal as well as 2 cm of the lateral orbital bony margin and a portion of the anterior temporalis muscle. Upper and lower eyelid skin flaps were preserved to help line the socket. The orbital lateral rim was reconstructed and the orbital cavity skin grafted.

Thirty-six hours postoperatively, he developed occipital pain and numbness, low back pain, and a fever of 39.2 C. Examination disclosed marked neck stiffness with a positive Kernig's sign, but no focal neurologic signs. The surgical wound was moderately edematous and erythematous, but there was minimal wound drainage.

Blood tests showed a leukocytosis. Cranial computed tomography did not show a wound, temporalis fossa, or intracranial abscess. Cerebrospinal fluid was cloudy with an opening pressure of 19.5 cm H_2O, protein level of 2,220 mg/l, and glucose level of 3.0 μmol/l (blood glucose level, 7.9 μmol/l). It contained 2.9×10^6/l white blood cells with 71% granulocytes, 5% lymphocytes, and 24% monocytes, but no bacteria on Gram stain.

Intravenous cloxacillin (2 g every four hours) and cefotaxime (2 g every six hours) were started. Within 12 hours, the neck pain and stiffness had lessened and his temperature returned to normal. Cerebrospinal fluid cultures grew *P. multocida*, sensitive to ampicillin, penicillin, chloramphenicol, erythromycin, and cefotaxime. The wound grew only *Staphylococcus epidermidis*. Three blood cultures were negative. Treatment was thus changed to intravenous penicillin (3 million units every four hours), but because of intolerance was later switched to intravenous and then oral chloramphenicol (500 mg every six hours) to complete 14 days of antibiotics. The patient remained well after treatment.

The patient owned a cat and a dog, which he nuzzled affectionately. The night before surgery he stayed with a friend whose dog licked his face and beard repeatedly. Oropharyngeal swabs from these pets yielded *P. multocida* from the cat only.

Pasteurella multocida is a small, nonmotile gram-negative coccobacillus isolated from the upper respiratory tract of 50% to 70% of healthy, domestic cats.[1] Unlike enteric gram-negative bacteria, it does not grow on MacConkey's agar[2] and is inhibited by penicillin.[1] It is resistant to erythromycin and aminoglycosides.[1] Chloramphenicol is the drug of choice in patients allergic to penicillin. There are no reports of treatment with the newer cephalosporins.

In the review by Weber and associates[4] of 34 cases of *P. multocida* infection, 21 patients had cellulitis. Those who contracted meningitis were either young (50% less than 1 year old) or elderly (30% over 60 years old). Our case is

unusual because of the patient's age and lack of skin involvement. The portal of entry was undoubtedly the exposed surgical site. Colonization probably took place in the oropharynx or conjunctiva.

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Traumatic Orbital Decompression

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A 34-year-old woman had a seven-year history of hyperthyroidism and a five-year history of bilateral proptosis with intermittent spontaneous subluxation of both globes in front of the eyelids. The patient was able to revert the eyelids manually and so did not seek medical attention for this problem.

Two years before we examined her she had been involved in a disagreement with her husband, who struck her about the right eye. Following this she noted improvement of the proptosis on that side, and no further episodes of subluxation of the globe. However, she continued to have subluxation of the left globe, which became increasingly frequent and more difficult to reverse. The patient recognized the therapeutic ocular effects achieved by the blow to her right eye, and would occasionally taunt her husband to similarly "fix" her left eye. He attempted this during another episode of domestic violence, but instead his blow resulted in a fracture of the patient's nose. Shortly thereafter, she and her husband were separated.

The patient then sought consultation. Exophthalmometry disclosed readings of 23 mm on the right side and 28 mm on the left. Palpebral fissures were 12 mm on the right and 16 mm on the left (Fig. 1). Orbital computed tomography demonstrated a blowout fracture of the right orbital floor with herniation of the orbital contents into the maxillary antrum (Fig. 2). We discussed treatment options of orbital decompression or lateral tarsorrhaphy for management of her left eye. She elected to undergo

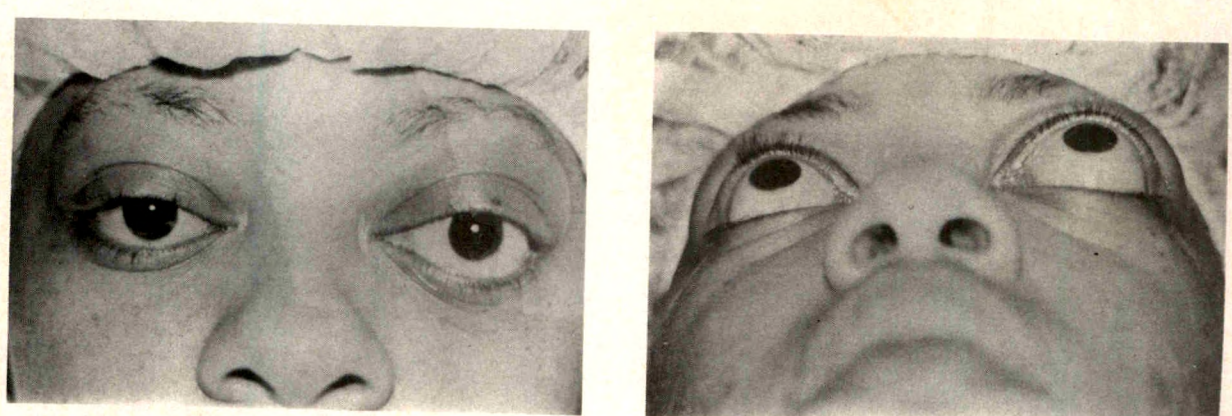


Fig. 1 (Kersten and Kulwin). Note the asymmetry of palpebral fissures (left), and proptosis (right) following a blow to the right orbit.

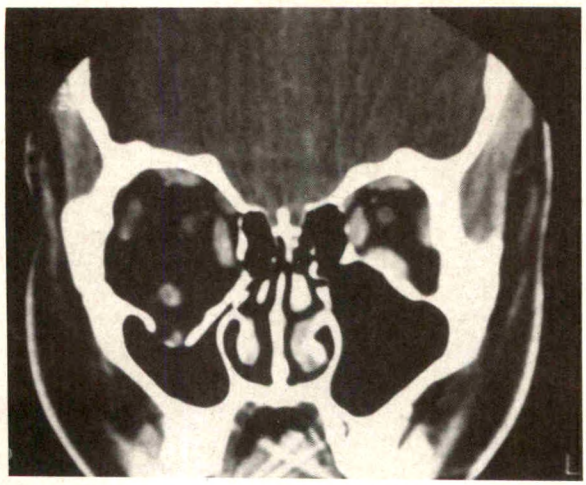


Fig. 2 (Kersten and Kulwin). Coronal computed tomography demonstrating blowout fracture of the right orbital floor with expansion of the right orbital volume and decompression of soft tissue into the maxillary sinus.

a left lateral tarsorrhaphy, and has not had any further episodes of subluxation.

Indications for orbital decompression in patients with Graves' ophthalmopathy include compressive optic neuropathy, severe proptosis with lagophthalmos and corneal exposure, and spontaneous luxation of the globes.[1] Because of difficulties in controlled administration, and potential adverse side effects,[2,3] periocular trauma cannot be considered a satisfactory approach for effecting orbital decompression in patients with Graves' ophthalmopathy and proptosis. However, the therapeutic effect that was achieved in this woman was interesting. The potential hazards of this nonsurgical decompression are exhibited by the outcome of the "procedure" subsequently attempted on the left.

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Orbital Roof Fracture With Ocular Herniation

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A 61-year-old man suffered a severe crush injury to his face when a tractor rolled over him. Profuse bleeding necessitated packing of the nasal cavity and oropharynx. On initial ocular examination, the patient was comatose, with marked facial swelling. The right eye was proptotic, with extensive subconjunctival hemorrhage and a reactive pupil. The anterior segment and fundus were normal. The left eyelids were swollen and the globe could not be found. Computed tomography of the head showed severe fragmentation of facial bones. The right optic canal appeared intact, but the left could not be defined. A round lucency in the left anterior cranial fossa was interpreted as the left eye (Fig. 1).

Four days after the injury, the patient was stable medically. Visual acuity was counting fingers in the right eye. A left frontal craniotomy was performed to evacuate a hematoma. The left eye was found, surrounded by orbital fat and brain, above a gaping defect in the orbital roof (Fig. 2). The globe and optic nerve appeared to be intact. The horizontal recti and

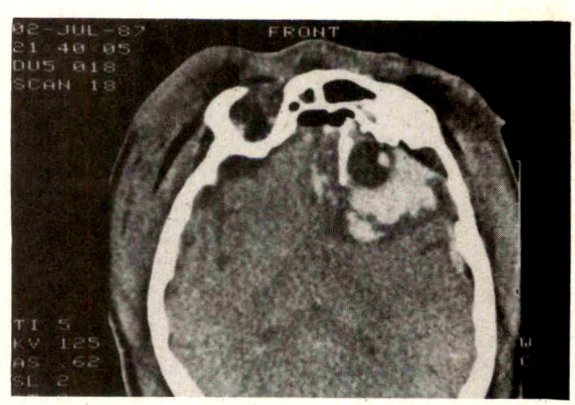


Fig. 1 (Ma and Nerad). Results of computed tomographic scan with contrast. The left eye is surrounded by an intracerebral hematoma in the left anterior cranial fossa. An air fluid level is present anteriorly. Obliteration of the cerebral sulci and ventricles indicates the space-occupying effect of the hematoma.

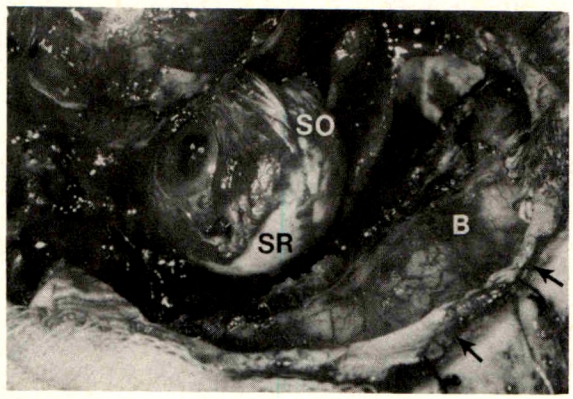


Fig. 2 (Ma and Nerad). Left anterolateral view of the eye in the left anterior cranial fossa during surgical exploration. Arrows indicate the margin of the cranial vault. B, left frontal lobe of the brain; SO and SR, stumps of avulsed superior oblique and superior recti muscles respectively.

inferior oblique muscles were attached; however, avulsed stumps of the vertical recti and superior oblique muscles were found. The pupil was unreactive to light, and there was no right consensual response. The eye was gently repositioned in the orbit and secured by suturing the avulsed stumps of the vertical recti muscles in the conjunctival fornices. The bony fragment of the orbital roof was repositioned, and autogenous fascia lata was grafted over the defect in the dura mater.

Postoperatively, the left eye occupied a normal position within the orbit. The left pupil remained unreactive and visual acuity was no light perception. Two months after the injury, visual acuity improved to 20/30 in the right eye, but remained no light perception in the left. The left eye was moderately enophthalmic. Inferior corneal scarring and a dense cataract that had developed prevented any view of the fundus.

A blowout fracture of the orbit occurs when a blow to the eye causes increased intraorbital pressure and herniation of orbital tissue through the relatively thin bone of the orbital floor or medial wall.[1] Complete displacement of the globe into the maxillary sinus has been described, with recovery of excellent vision after repositioning of the eye.[2] In contrast, the thicker orbital roof is usually only breached by large direct forces to the skull, often in the context of multiple craniofacial injuries.[3] Superior blowout fractures without fracture of the orbital rim may occur in patients with unusual posterior extensions of the frontal sinuses resulting in a particularly thin orbital roof.

We decided to explore for the left eye because it appeared to be intact and because we wanted to preserve any remaining vision in that eye. The eye was intact macroscopically when examined in the cranial cavity, but we could not exclude such causes of blindness as traumatic or ischemic optic neuropathy, or arterial occlusion. We considered the likelihood of anterior segment ischemia to be small, since Hayreh and Scott[4] have demonstrated that the anterior ciliary circulation is adequate if two recti muscles with their ciliary arteries remain attached to the eye. Although the posterior circulation could not be assessed, the globe was replaced in the orbit with reasonable hope for survival and, possibly, vision. After six months, there is still no vision in the left eye, although it appears to be viable.

We believe that an attempt should be made to reposition an intact eye that has herniated into the brain, even though our experience with this patient suggests that any trauma which can cause roof fracture and superior herniation is also likely to damage the eye or optic nerve seriously.

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A New Intra-anterior Chamber Iris Suturing Method

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Successful posterior chamber lens implantation is difficult to achieve in a pupil that is miotic because of long-term administration of a cholinergic agent or other causes. For a successful operation, sufficient pupil area must be achieved by peripheral iridectomy combined with radial iridotomy. Iris suturing is often used to prevent postoperative glare; however, when the surgeon retracts the inflexible iris outside the anterior chamber, various complications may result, such as fragmentation, bleeding, or iridodialysis. Furthermore, because of excessive iris damage, postoperative inflammation may be severe and prolonged. For these reasons, iris suturing should be done inside the anterior chamber. We have devised a new intra-anterior chamber iris suturing method.

After achieving sufficient pupil area via iridectomy and iridotomy, planned extracapsular cataract extraction and posterior chamber lens implantation are performed with 1% sodium hyaluronate; interrupted sutures are then placed in the corneoscleral wound, leaving a 3- to 4-mm opening (Fig. 1). A straight needle with 10-0 polypropylene suture is threaded across the severed iridectomy with forceps (Fig. 1, top left). Both suture ends are then drawn out of the wound opening. The first tie, a double-loop knot, is made outside the anterior chamber. Passing one strand through the eye of a small sewing needle (Fig. 1, top right), then holding the needle eye at the pupil edge inside the anterior chamber while pulling the two strands, the surgeon ties the first loop (Fig. 1, middle left). The second loop, made outside the anterior chamber (Fig. 1, middle right), is then tied in a similar manner to complete the knot (Fig. 1, bottom left). The suture ends are cut as close to the knot as possible with Vannas scissors (Fig. 1, bottom right).

Since such a knot is located on the anterior surface of the iris, there is risk of damage to the corneal endothelium. If the surgeon wishes to place the knot on the posterior surface of the iris, a slightly modified procedure is needed (Fig. 2). A straight needle, bent to a diameter of about 15 mm, is introduced via the right side of the wound, the left edge of the iris is pierced from back to front, and the needle is passed out through the left side of the wound (Fig. 2, top left). The needle is then reversed and passed through to the opposite side of the wound (Fig. 2, top right). Reintroduced from that side, the

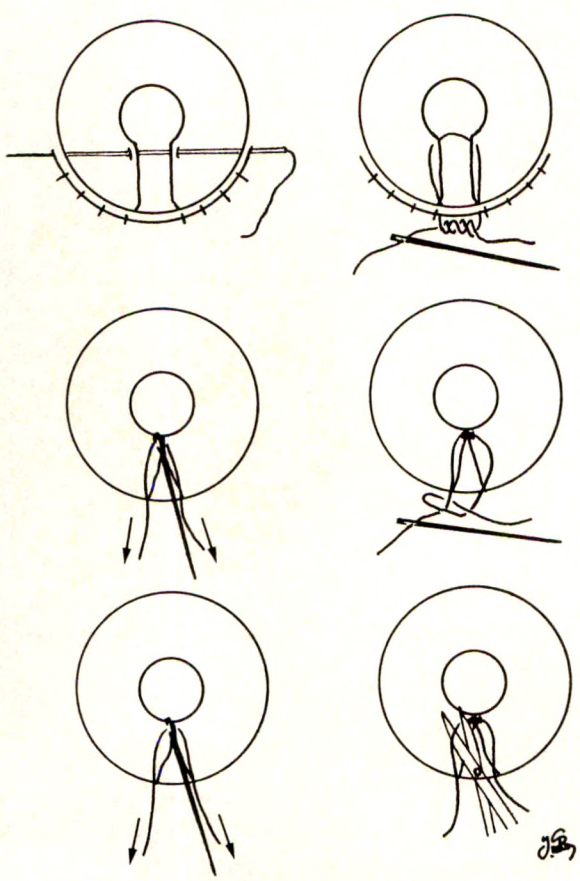


Fig. 1 (Saito and Kiboshi). Iris suturing inside the anterior chamber (knot is placed on the anterior surface of the iris).

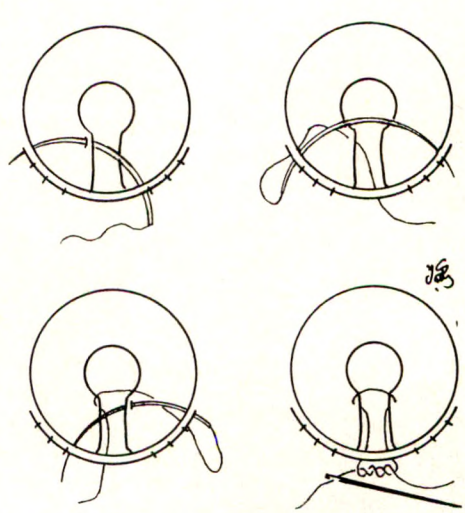


Fig. 2 (Saito and Kiboshi). Iris suturing inside the anterior chamber (knot is placed on the posterior surface of the iris).

needle pierces the right edge of the iris from front to back (Fig. 2, bottom). Subsequently, the procedure is the same as for the conventional method (Fig. 1).

These procedures are indicated for the eye with an inflexible, fragile, easily fragmentable iris and a fibrosed, miotic pupil. It is easy to suture the iris inside the anterior chamber without tractional force; second and later suture knots are also easily done. We recommend these procedures for safe posterior chamber lens implantation in cases of miotic pupil.

Changing Utilization of Donor Corneas

Emile J. Farge, Ph.D.

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Inquiries to Emile J. Farge, Ph.D., Baylor College of Medicine, 6501 Fannin, Houston, TX 77030.

Eye banks began in the 1940s in response to the need of ophthalmologists to provide corneal tissue for patients requiring keratoplasty.[1-3] The volume and number of eye banks have grown in the past four decades. Approximately 200 keratoplasties were performed in 1946, whereas more than 28,000 corneal grafts were performed in the U.S. during 1986, according to member activity published in 1987 by the Eye Bank Association.

The need for lenticules for epikeratophakia and other refractive keratoplasty procedures has brought a change in eye banking. In order to chart the growth of donor cornea distribution, we reviewed our experience at the Lions Eyes of Texas Eye Bank, Houston. Our service area covers an area of 26 Texas counties containing just over 4 million persons. There are about 400 ophthalmologists in the area, approximately 25% of whom perform corneal surgery. Donor corneas are distributed to regional ophthalmologists, and additional tissue is provided to eye banks and hospitals in other parts of the country and the world.

In the first five-year interval 6,924 corneas were distributed for penetrating or lamellar keratoplasty and none for refractive surgery (Table). During 1983 to 1987, 1,340 (7%) of all donor tissue was used for refractive keratoplasty, principally epikeratophakia. Although this change has not yet affected utilization of donor corneas for penetrating keratoplasty, eye banks must continue to reevaluate the needs of patients and ophthalmologists.

TABLE
DONOR CORNEA DISTRIBUTION IN HOUSTON, 1978–1987

	1978–1982		1983–1987	
TYPE	NO.	(%)	NO.	(%)
Penetrating keratoplasty (local)	2,373	(27)	3,497	(20)
Penetrating keratoplasty (exported)	4,551	(51)	7,773	(43)
Refractive keratoplasty	0	(0)	1,340	(7)
Nonsurgical	1,938	(22)	5,283	(30)

References

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2. Cordes, F. C.: The Eye Bank Committee. Am. J. Ophthalmol. 43:310, 1957.
3. Farge, E. J.: The Eye Bank Association of America, history and development. In Brightbill, F. S. (ed.): Corneal Surgery. St. Louis, C. V. Mosby, 1986, pp. 673–678.

Hyperkeratinization in a Rabbit Model of Meibomian Gland Dysfunction

Robert Lambert, Ph.D., and Ronald E. Smith, M.D.

Department of Ophthalmology, University of Southern California School of Medicine and Estelle Doheny Eye Institute. This study was supported in part by National Institutes of Health Core Center grant E-03040 and a grant from Research to Prevent Blindness, Inc.

Inquiries to Ronald E. Smith, M.D., Estelle Doheny Eye Institute, 1355 San Pablo St., Los Angeles, CA 90033.

In 1981, Jester, Nicolaides, and Smith[1] described a model of meibomian gland dysfunction, features of which included erythema of the conjunctiva, hyperkeratinization of meibomian gland ductal epithelium, plugging of the meibomian gland orifice with retention of gland material, and swelling of the gland lumen. Although the surface characteristics of the eyelid margin and orifices were not reported, the model provided support for the hypothesis that meibomian gland dysfunction is in-

volved in the pathogenesis of blepharoconjunctivitis. We studied the surface structure of the eyelid margin before and during the development of meibomian gland dysfunction in this model.

We used two groups of New Zealand albino rabbits. An experimental group (n = 6) received one drop of 2% epinephrine hydrochloride in both eyes twice daily for 24 weeks. A control group (n = 6) did not receive any drugs. The eyelid margins were examined routinely using a hand-held lens. Morphologic changes in meibomian gland structure were documented by transilluminated biomicroscopy as described by Jester and colleagues.[2] After the animals were killed, the eyelids were removed, bisected, and processed for light and scanning electron microscopy.

Examination of tissue from control animals showed no histopathologic abnormalities. Scanning electron microscopy of the eyelid margin showed a prominent external orifice of the meibomian gland located at the mucocutaneous junction. The area directly adjacent to the orifice was clear of desquamated keratinized epithelium, which appeared to be localized at the base of the eyelashes (Fig. 1). This appearance contrasted sharply with scanning electron microscopy observations of eyelid margin tissue from animals treated with topical 2% epinephrine. In all treated animals, the surface area occupied by desquamated keratinized epithelium was increased dramatically. The epithelium frequently extended from the base of the eyelashes to the mucocutaneous epithelial junction as a thick continuous "mantle" of cells (Fig. 2). Surface features around the external orifice of meibomian glands were routinely obliterated. Histopathologic examination of treated material confirmed the existence of a thickened ductal epithelium at the external orifice of dysfunctional glands.

The abundance of desquamated epithelium on the eyelid margin represents a new observation regarding the epinephrine-induced model

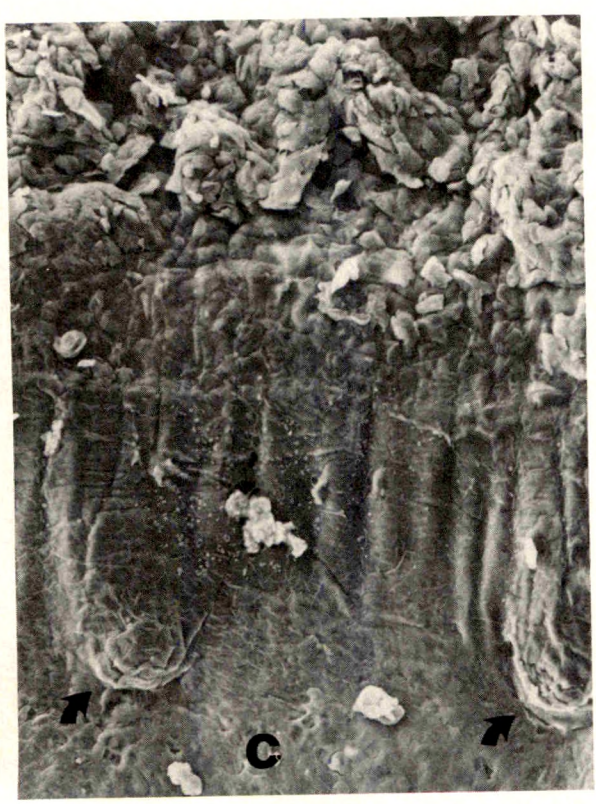


Fig. 1 (Lambert and Smith). Scanning electron micrograph of the conjunctival surface (c) and normal rabbit eyelid. Desquamated epithelium is present at the base of the eyelashes but does not extend to the level of the meibomian gland orifice (arrows) (×90).

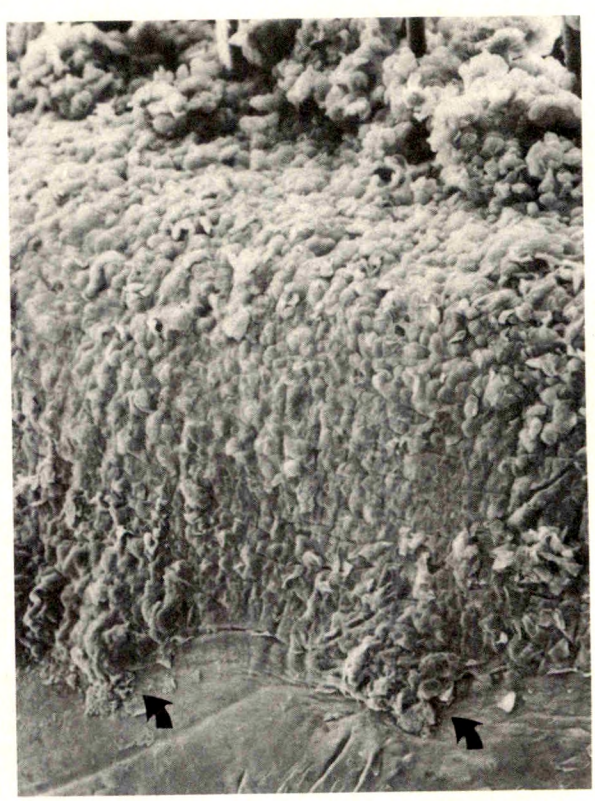


Fig. 2 (Lambert and Smith). At an advanced stage of meibomian gland dysfunction, desquamated keratinized epithelium proliferates to the level of the meibomian gland orifice (arrows) (scanning electron microscopy, ×130).

of meibomian gland dysfunction. Proliferation of desquamated epithelium probably occurs as a sequelae to hyperkeratinization of ductal epithelium and results in a loss of patency of the gland orifice. An occlusion of the external orifice of the meibomian gland with desquamated epithelium may further inhibit the expression of meibomian gland material. If similar changes occur in patients with blepharitis, it would be appropriate to treat this disorder, in part, by proposing regular scrubbing of the eyelid margin to remove excess debris, which would include keratinized cells.

References

1. Jester, J. V., Nicolaides, N., and Smith, R. E.: Meibomian gland studies. Histologic and ultrastructural investigations. Invest. Ophthalmol. Vis. Sci. 20:537, 1981.

2. Jester, J. V., Rife, L., Nii, D., Luttrull, J. K., Wilson, L., and Smith, R. E.: In vivo biomicroscopy and photography of meibomian glands in a rabbit model of meibomian gland dysfunction. Invest. Ophthalmol. Vis. Sci. 22:660, 1982.

Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Extracapsular Cataract Extraction and Posterior Chamber Intraocular Lens Implantation Combined With Trabeculectomy in Patients With Glaucoma

EDITOR:

In the article, "Extracapsular cataract extraction and posterior chamber intraocular lens implantation combined with trabeculectomy in patients with glaucoma," by S. T. Simmons, D. Littoff, D. A. Nichols, M. B. Sherwood, and G. L. Spaeth (Am. J. Ophthalmol. 104:465, November 1987), I was surprised by two points:

The authors did not cite an article on this subject, which I published in the French literature together with my colleagues.[1]

Also, the authors did not refer to any other type of intervention, such as separate incisions for the extraction of the lens and the trabeculectomy. Separate incisions may decrease the risk of inflammation and hyphema, and may assure more permeability of the trabeculectomy.

I was also surprised by the absence of secondary subluxation of the intraocular lens and modification of the size and aspect of the pupil, except in one case.

DAN A. LEBUISSON, M.D.
Neuilly-sur-Seine, France

Reference

1. Lebuisson, D., Delbecque, P., Leroy, L., Montin, J.-F., and Bamba, M.: L'opération combinée. Cataracte et glaucome avec implantation. Résultats d'une série de 28 cas. J. Fr. Ophtalmol. 7:781, 1984.

Reply

EDITOR:

We thank Dr. Lebuisson for his interest and comments about our article. This study was undertaken to review our results in patients undergoing combined cataract extraction and trabeculectomy performed in the manner outlined in the paper. The investigation concentrated on intraocular pressure control and visual results, and these were reported. The purpose of this paper was not to review this topic or to compare this surgical approach to others because only a prospective, randomized trial can clearly address these issues. We regret our oversight in not citing Dr. Lebuisson's publication in our references and again appreciate his interest and comments.

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Philadelphia, Pennsylvania
and Albany, New York
DAVID LITOFF, B.A.
Albany, New York
DAN A. NICHOLS, M.D.
MARK B. SHERWOOD, M.D.
GEORGE L. SPAETH, M.D.
Philadelphia, Pennsylvania

Positional Changes in the Vasculature of the Optic Disk in Glaucoma

EDITOR:

In the article, "Positional changes in the vasculature of the optic disk in glaucoma," by R. Varma, G. L. Spaeth, C. Hanau, W. C. Steinmann, and R. M. Feldman (Am. J. Ophthalmol. 104:457, November 1987), the ability to detect a change in the position of optic disk blood vessels was estimated using both image analysis and clinical observation of optic disk monophotographs. Of 34 sets of optic disk photographs from 19 patients with glaucoma, image analysis showed positional centrifugal shifts of the blood vessels in 16 optic disks, whereas the clinicians noted these changes in only seven optic disks.

These results are in very good agreement with ours.[1] In a group of 46 patients with ocular hypertension followed up prospectively for five to 7.5 years, we noted a slight increase in disk cupping on stereophotography in 19 patients. In nine of these patients, progression was detected by monoscopic evaluation of the photographs, which was always done before the stereoscopic evaluation. The most frequent findings were small deflections in the vessels on the disk, which showed loss of disk tissue.

Thus, stereophotography of the optic disk seems to be just as good as the more elaborate image analysis of monophotographs in detecting small increases in disk cupping in glaucoma.

TOR ODBERG, M.D.
DAG RIISE, M.D.
Hamar, Norway

Reference

1. Odberg, T., and Riise, D.: Early diagnosis of glaucoma. Acta Ophthalmol. 63:257, 1985.

Reply

EDITOR:

We thank Drs. Odberg and Riise for their comments. It is interesting to note the similarity between their results and ours despite the different populations and methodology. Neither study, however, can answer the question of the comparative sensitivity of clinical evaluation of stereophotographs and image analysis. Therefore, it cannot be said that stereophotography of the optic disk is "just as good as the more elaborate image analysis of monophotographs in detecting small increases in disk cupping in glaucoma."

If Drs. Odberg and Riise were to send the optic disk photographs of their 46 patients to us for image analysis, perhaps then we could answer the question they have raised; that is, is the sensitivity in detection of vessel shift using image analysis of monoscopic photographs similar to that of clinical evaluation of stereoscopic photographs?

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GEORGE L. SPAETH, M.D.
CHERYL HANAU, B.S.
WILLIAM C. STEINMANN, M.D.
ROBERT M. FELDMAN, M.D.
Philadelphia, Pennsylvania

Low-Contrast Letter Charts to Detect Subtle Neuropathies—Correction

EDITOR:

The title of our article (Am. J. Ophthalmol. 105:141, February 1988) should have read "Low-Contrast Letter Charts to Detect Subtle Optic Neuropathies."

MITCHELL D. DRUCKER, M.D.
PETER J. SAVINO, M.D.
ROBERT C. SERGOTT, M.D.
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Philadelphia, Pennsylvania
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Seattle, Washington

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Retinitis Pigmentosa. By John R. Heckenlively. Philadelphia, J. B. Lippincott Company, 1988. 352 pages, index, illustrated. $67.50

Reviewed by RICHARD A. LEWIS
Houston, Texas

"Where can I read about retinitis pigmentosa?" Until recently, the questioner would be directed to any number of primary references, most of which were limited by the biases of the senior author, restricted to small series, or dated. Heckenlively's book, however, offers a new and succinct answer to the question and provides a scholarly and informed overview of the numerous diagnostic entities clustered under the umbrella of retinitis pigmentosa. Heckenlively himself has authored or coauthored every chapter in this text, save one. Chapter 1 summarizes the definition of retinitis pigmentosa reached several years ago by a consensus panel and reviews the diagnostic breadth of these diseases. Chapter 2 details the diagnosis and classification of the diseases, including the standard electrophysiologic and psychophysiologic tests and the interpretation of family history and pedigree analysis. Additional chapters summarize visual field findings in retinitis pigmentosa, the current knowledge of histopathology and cellular mechanisms in retinitis pigmentosa, and the clinical features of the disease. Chapter 6, "Management and Treatment of Retinitis Pigmentosa," is perhaps the most important chapter in the text. It presents the routine evaluation of a patient with pigmentary retinopathy and provides excellent guidelines for cataract surgery in the patient with retinitis pigmentosa, family counseling, low-vision aids, and an appendix of agencies that offer services or information to the visually impaired. Other chapters cover congenital and early onset forms of retinitis pigmentosa, dominant, recessive, and X-linked forms, syndromes related to retinitis pigmentosa, and the nonhereditary pigmentary retinopathies. Richard Weleber and Nancy Kennaway have contributed a superb chapter of the current understanding of gyrate atrophy of the retina and choroid.

The text is lucid and compact. It is beautifully illustrated by the liberal use of color photographs, most of them of superb quality.

There are occasional frustrating limitations. Most of the automated visual fields are presented by computer abstraction in gray tones, rather than the more informative decibel scales. In some tables, where studies of the 900 retinitis pigmentosa cases in the UCLA Retinitis Pigmentosa Registry are summarized, the percentages of specific features are not correlated for age or analyzed by life-table analysis. In the discussion of recessive variants of retinitis pigmentosa, there is a confusion in the text between fundus albipunctatus, a nearly stationary disorder, with retinitis punctata albescens, a progressive and degenerative disorder. The chapter on gyrate atrophy unfortunately does not follow the electrophysiologic descriptions and format of the rest of the text, particularly the introductory Chapter 2. In the discussion of syndromes, a few diseases without progressive degeneration are included, such as Waardenburg's syndrome and incontinentia pigmenti, although they have no direct bearing on retinitis pigmentosa. Despite the outstanding quality of the text and textual editing, a number of fundus photographs are presented inverted and reversed, apparently mostly those taken on wide-field fundus formats.

These criticisms apply only to a small portion of the otherwise excellent, timely, and complete book. Anyone, whether in residency or in practice, who has an interest in the current state of this occasionally confusing, but extremely important, clinical entity will find this handsome volume a valuable resource for years to come.

Neuro-ophthalmology. A Problem-Oriented Approach. By Roy W. Beck and Craig H. Smith. Boston, Little Brown and Co., 1987. 264 pages, index, illustrated. $39.50

Reviewed by MYLES M. BEHRENS
New York, New York

The authors have set out to provide a broad overview of neuro-ophthalmology, using case studies to illustrate various aspects of the entities most commonly encountered. They stress

the importance of the neuro-ophthalmic history and examination in reaching a diagnosis and include practical discussions of differential diagnosis, management, and prognosis. They have produced an excellent, well written, and very readable book that is well illustrated, well referenced, and well indexed. It is, however, not without its share of errors and omissions, most of which will, I'm sure, be corrected in the next edition. It is not the complete text the resident wants and it is not an advanced text suitable for neuro-ophthalmologists, but it is just the thing for practicing ophthalmologists and neurologists and would serve as valuable additional reading or review material for residents. The table of contents is sufficient to guide the reader to any of the useful clinical capsules.

Retinal Diseases. Biomedical Foundations and Clinical Management. By Mark O. M. Tso. Philadelphia, J. B. Lippincott Company, 1988. 480 pages, index, illustrated. $65

Reviewed by CHRISTOPHER F. BLODI
Iowa City, Iowa

Many of the chapters in this book contain useful information on medical and surgical aspects of retinal disorders. The text summarizes the proceedings of an international symposium held in Taipei, Taiwan, in the summer of 1983, covering both the clinical and basic science aspects of recent research in retinal diseases.

As with other compilations of meetings, the problems of timeliness and of quality varying from chapter to chapter come to the surface. Some of the authors have obviously updated their papers, since many references that postdate the meeting are included in several of the chapters.

Certain chapters will stand out for all ophthalmologists interested in retinal diseases. Tso's chapters on retinal light toxicity and on cystoid macular edema are extraordinarily complete and up-to-date. Blumenkranz's discussion of the surgical treatment of complicated retinal detachment is a clearly written summary of the author's own approach to this severe and complex problem.

The wide ranging subject matter covered in Retinal Diseases will be most interesting to ophthalmologists with a special interest in retinal diseases.

Books Received

Ophthalmic Drug Delivery. Edited by M. F. Saettone, M. Bucci, and P. Speiser. Padova, Italy, Liviana Editrice S.p.A., 1987. 195 pages, index, illustrated. $59.50

These papers were presented at an international symposium on ophthalmic drug delivery held in Pisa, Italy, in October 1986.

Evoked Potentials III. The Third International Evoked Potentials Symposium. Edited by Colin Barber and Thomas Blum. Stoneham, Massachusetts, Butterworths, 1987. 487 pages, index, illustrated. $98

This volume records the proceedings of an international symposium on evoked potentials held in Berlin in 1986. It is a startling demonstration of the extent to which this field has grown. Sixty-eight papers by 189 authors are included. The book has been carefully assembled and pleasingly designed. Anyone who works with evoked potentials should have it as a reference work.

ABSTRACT DEPARTMENT

Edited by David Shoch, M.D.

British Journal of Ophthalmology

Anterior segment ischaemia following laser photocoagulation in a patient with systemic lupus erythematosus. Jost, B. F., Olk, R. J., Patz, A., Fine, S. L., and Murphy, R. P. (4949 Barnes Hosp. Plaza, East Pavilion Suite 17413, St. Louis, MO 63110). Br. J. Ophthalmol. 72:11, 1988.

A 44-year-old woman with a six-year history of systemic lupus erythematosus was seen for blurring of vision caused by neovascularization of the retina. Approximately 1,000 applications of argon laser photocoagulation were applied to the eye after administration of topical anesthesia. A Goldmann three-mirror lens was used and the procedure took about 30 minutes. Two days later the patient had an acutely inflamed, tender right eye, with marked chemosis and corneal edema. A diagnosis of anterior segment ischemia was made. The eye gradually quieted but was left with an atrophic iris and neovascularization. The photocoagulation was thought to be an insult to an eye already ischemic as the result of systemic lupus erythematosus. The authors suggested that patients with systemic lupus erythematosus receiving photocoagulation should be carefully examined for evidence of anterior ischemia, that the panretinal photocoagulation be done in separate sessions, and that any undue pressure with the contact lens should be avoided. (7 figures, 37 references)—David Shoch

Cancer

Reversible ocular toxicity related to tamoxifen therapy. Ashford, A. R., Donev, I., Tiwari, R. P., and Garrett, T. J. (Dept. Med., Harlem Hosp. Ctr., 506 Lenox Ave., New York, NY 10037). Cancer 61:33, 1988.

The patient described in this report developed ocular symptoms three weeks after starting a low dose of tamoxifen daily. Ocular examination showed bilateral optic disk swelling and diffuse retinal hemorrhages. Repeated cerebrospinal fluid examinations showed no malignant cells and normal pressures. There were no other neurologic findings and no radiologic evidence of metastases to the brain. The tamoxifen was discontinued and within two weeks the visual symptoms had cleared; within three months the fundi were normal. Tamoxifen is widely used for the treatment of metastases in breast cancer, and periodic ophthalmologic examination is advised. (2 figures, 14 references)—David Shoch

Journal of Computer Assisted Tomography

CT demonstration of extraocular muscle atrophy. Hansman, M. L., Peyster, R. G., Heiman-Patterson, T., and Greenfield, V. S. (Dept. Diagnostic Radiol., Hahnemann Univ. Hosp., Mail Stop # 206, Broad and Vine Streets, Philadelphia, PA 19102). J. Comput. Assist. Tomogr. 12:49, 1988.

The authors described two patients who had extraocular muscle atrophy noted on computed tomography. The first patient had decreased vision and third, fourth, and sixth nerve palsies from a calcified lesion of the posterior cavernous sinus. The second patient had a 13-year history of progressive bilateral ophthalmoplegia associated with Kearns-Sayre syndrome. In the first case there was marked atrophy of the extraocular muscles seen best on coronal view, whereas in the second case there was bilateral extraocular muscle atrophy. Although previous studies in cases of nerve palsies have not shown any wasting of the extraocular muscles, the authors suggested that the muscle wasting in the first case was the result of the long-term paralysis. Muscle wasting of the extraocular muscles has not been described before in the Kearns-Sayre syndrome, but previous reports have indicated that there is a diffuse loss of muscle fibers and an increase in

the loose connective tissue and fat. It is not known whether Kearns-Sayre syndrome is caused by a myopathy or nerve involvement. (2 figures, 11 references)—David Shoch

Journal of Neurosurgery

Optic nerve decompression in osteopetrosis. Al-Mefty, O., Fox, J. L., Al-Rodhan, N., and Dew, J. H. (Dept. Neurosurg., Univ. Mississippi Med. Ctr., 2500 N. State St., Jackson, MS 39216-4505). J. Neurosurg. 68:80, 1988.

Osteopetrosis is a group of disorders linked by defective osteoclastic function. Osteopetrosis causes thickening and increased density of the skull and the most common neurologic finding is optic atrophy from optic nerve compression in the canal. However, retinal degeneration has also been described in osteopetrosis and it is hypothesized that it is this degeneration and not the compression of the optic nerve in the canal which causes the visual loss. In six patients with osteopetrosis and severe loss of vision, all had bilateral optic nerve decompression through a supraorbital craniotomy. One patient was lost to follow-up. The remaining five patients showed stabilization of their vision and in one case there was a remarkable improvement from counting fingers to 20/40 in the right eye and 20/70 to 20/40 in the left eye. The remaining four patients showed at best about one line of improvement. The authors emphasized the need for a wide unroofing of the optic canals. (5 figures, 1 table, 39 references)—David Shoch

Gliomas of the optic nerve or chiasm. Outcome by patients' age, tumor site, and treatment. Alvord, E. C., Jr., and Lofton, S. (Neuropath., Univ. Washington School of Med., Seattle, WA 98195). J. Neurosurg. 68:85, 1988.

A review of the literature revealed 623 cases of optic gliomas with sufficient information to permit actuarial (life-table) analysis concerning the prognosis of this disease by the patients' age, tumor site, treatment, and presence of concomitant neurofibromatosis or extension into the hypothalamus or ventricle. All of these factors are important. The development of mathematical models led to the conclusion that these tumors, generally regarded histologically as low-grade astrocytomas, actually have a very wide but continuous range of growth rates. Some grow rapidly enough to be explained by simple exponential doubling at a constant rate, but most behave as though their growth decelerates. Decelerating growth rates make comparisons of various groups of patients difficult. No support is found for the classical hypothesis that some may be hamartomas.

Inadequately treated gliomas of the optic nerve or chiasm bear about the same poor prognosis. However, tumors of the optic nerve (intracranial as well as intraorbital) have an excellent prognosis following complete surgical excision and only a slightly poorer prognosis following irradiation. About 5% of optic nerve gliomas recur in the chiasm following "complete" intraorbital excision. Patients with neurofibromatosis have about twice the recurrence rate following complete excision of an intraorbital glioma. Optic chiasmal gliomas appear to respond to irradiation with doses above 4500 rads. Patients with neurofibromatosis have about the same prognosis as patients without neurofibromatosis following irradiation of a chiasmal glioma. (11 figures, 6 tables, 107 references)—Authors' abstract

Journal of Pediatric Ophthalmology and Strabismus

Ten years without orbital optic nerve: Late clinical results after removal of retrobulbar gliomas with preservation of blind eyes. Wolter, J. R. (Dept. Ophthalmol., Univ. Michigan Hosp., Ann Arbor, MI 48105). J. Pediatr. Ophthalmol. Strabismus 25:55, 1988.

Orbital optic gliomas, in contrast to chiasmal optic gliomas, have a relatively benign prognosis for life and there are occasional cases in which the glioma can be demonstrated to be completely free of the optic canal and therefore excisable. Eyes with orbital optic gliomas are

often blind and the usual course has been to enucleate the eye and remove the glioma. The author points out that one can use a transconjunctival lateral approach and prolapse the glioma into the space just created and spare the globe. He reports two cases in which this was done and although the central retinal artery was removed, the eyes maintained reasonable health, even though a vulnerable corneal surface and positional abnormalities remained. However, the preservation of the eye may prevent deformation of the orbit and asymmetric facial growth. (10 figures, 7 references)—David Shoch

New England Journal of Medicine

Prophylaxis of gonococcal and chlamydial ophthalmia neonatorum. Laga, M., Plummer, F. A., Piot, P., Datta, P., Namaara, W., Ndinya-Achola, J. O., Nzanze, H., Maitha, G., Ronald, A. R., Pamba, H. O., and Brunham, R. C. (Dept. Microbiol., Inst. Tropical Med., Nationalestraat 155, 2000 Antwerp, Belgium). N. Engl. J. Med. 318:653, 1988.

We evaluated the use of silver nitrate drops and tetracycline ointment for the prophylaxis of ophthalmia neonatorum in a controlled trial involving 2732 newborns in Nairobi, Kenya. The overall rates of prevalence of intrapartum maternal gonococcal and chlamydial infection were 6.4 and 8.9 percent, respectively. After prophylaxis with silver nitrate, the incidence rates of gonococcal, chlamydial, and nongonococcal, nonchlamydial ophthalmia neonatorum were 0.4, 0.7, and 6.2 percent, respectively, whereas after prophylaxis with tetracycline, the rates were 0.1, 0.5, and 4.5 percent. The attack rates of gonococcal ophthalmia neonatorum in newborns exposed to *Neisseria gonorrhoeae* at birth were 7.0 percent in those receiving silver nitrate and 3.0 percent in those receiving tetracycline (95 percent confidence interval for the difference in rates, −3.4 to 11.4 percent). As compared with historical controls, the incidence of gonococcal ophthalmia neonatorum decreased 83 percent among infants treated with silver nitrate and 93 percent among those treated with tetracycline. Failure of prophylaxis was associated with postpartum maternal endometritis ($P = 0.05$).

Among newborns exposed to maternal infection with *Chlamydia trachomatis*, chlamydial conjunctivitis developed in 10.1 percent given silver nitrate and in 7.2 percent given tetracycline (95 percent confidence interval for the difference in rates, −4.7 to 10.5 percent), yielding reductions in the incidence of chlamydial ophthalmia of 68 and 77 percent, respectively, as compared with the historical controls.

We conclude that tetracycline is as effective as silver nitrate in preventing gonococcal ophthalmia neonatorum. (4 tables, 28 references)—Authors' abstract

Retina

The blood-retinal barrier in Berlin's edema. Pulido, J. S., and Blair, N. P. (Univ. Ill. Eye and Ear Infirm., 1855 W. Taylor St., Chicago, IL 60612). Retina 7:233, 1987.

The authors made an ophthalmoscopic diagnosis of Berlin's edema in ten patients who suffered blunt trauma to the eye. All of the patients had retinal whitening and visual loss characteristic of Berlin's edema. All were examined with fluorescein angiography and vitreous fluorophotometry. In all cases, results of fluorescein angiography were normal and there was no difference in the vitreous fluorometric findings from normals in the same laboratory. The authors thus concluded that there was no break in the blood-retinal barrier in Berlin's edema and that the visual loss and the ophthalmoscopic findings were probably caused by deformation of the vitreous while it was expanding and contracting during blunt trauma; this might then have resulted in intracellular disruption. Since there was no breakdown of the barrier, they suggested that this condition be termed commotio retinae. (1 table, 9 references)—David Shoch

Survey of Ophthalmology

Solar radiation and age-related macular degeneration. Young, R. W. (Dept. Anatomy, UCLA Med. School, Los Angeles, CA 90024-1763). Surv. Ophthalmol. 32:252, 1988.

Age-related macular degeneration appears to be largely limited to the outer layers of the retina and particularly the layers in the macular area of the posterior pole. There is a disruption of the pigment epithelium, with secondary involvement of the overlying photoreceptors. Studies on radiation injury to the eye also show that the damage is greatest in the outer layers of the retina and at the posterior pole. As might be expected, the high energy portion of the spectrum appears to be most effective in causing this damage, particularly the blue-violet and ultraviolet wavelengths. The lesion may be related to the photodynamic effects of free radicals in the tissues. The eye may be protected from radiation damage by the presence of a dense cataract or by large amounts of melanin. Thus, people with dark irides and those with increased melanin pigment in the choroid tend to be more resistent to radiation damage. Together, these characteristics seem to implicate radiant energy as a major factor in the development of age-related macular degeneration. The author recommends a normal diet in the elderly, including antioxidants such as vitamin C, vitamin E, and betacarotene. Further, in bright sunlight, sunglasses that eliminate wavelengths below 500 nm might be advisable. (1 figure, 299 references)—David Shoch

Transactions of the American Ophthalmological Society

All of the following are summaries of theses published in the "Transactions of the American Ophthalmological Society."

Oxygen therapy and intraocular oxygenation. Jampol, L. M. (Dept. Ophthalmol., Northwestern Univ. Med. School, 303 E. Chicago Ave., Chicago, IL 60611). Trans. Am. Ophthalmol. Soc. 85:407, 1987.

It has been postulated that ischemic disease of the anterior segment and perhaps the posterior segment of the eye might be ameliorated by increased oxygen levels within the eye. If 100% oxygen was delivered to the rabbit cornea through close-fitting goggles, the oxygen tension of the aqueous humor was raised significantly. The oxygen tension was raised even further when the pressure of the surrounding atmosphere was raised to 2 atm. The high oxygen levels obtained under these hyperbaric conditions were mediated both through the concentration of oxygen in the blood and by transcorneal delivery of oxygen. Delivery to the anterior segment is of potential import to patients with sickle cell anemia, since it can prevent sickling of erythrocytes in the anterior chamber and thus avoid the serious complication of sickle cell glaucoma. The author also showed that the preretinal vitreous levels of oxygen were increased by exposing the rabbit cornea to 100% oxygen via tight-fitting goggles. The delivery of oxygen to the anterior segment may be of benefit to patients with posterior ischemic disease, particularly if the disease is transient in nature. (8 figures, 5 tables, 47 references)—David Shoch

RP cone-rod degeneration. Heckenlively, J. R. (Jules Stein Eye Inst., UCLA School of Med., Los Angeles, CA 90024). Trans. Am. Ophthalmol. Soc. 85:438, 1987.

Retinitis pigmentosa has traditionally been thought of as a rod-cone dystrophy where the rods are more severely affected than the cones and, therefore, the scotopic electroretinogram is more severely depressed than the photopic electroretinogram. Because in some patients the photopic response is depressed more than the scotopic response, the author systematically studied a large group of patients, all of whom had been characterized as having retinitis pigmentosa. A subgroup showed a definite cone-rod pattern. In these cone-rod patients the rod response was larger than the cone response, although both were depressed. As the disease progressed, the rod and cone response became approximately equal and eventually the electroretinogram became nonrecordable using a single-flash technique. There was good residual rod function until the visual field was reduced to less than 10 degrees. In the final stages of retinitis pigmentosa, the cone-rod patients became night blind and it was

difficult to distinguish them from the typical advanced patients with rod-cone degeneration. In general, the pigmentary changes seemed to correlate with electroretinogram parameters. However, in patients with heavy pigmentation, the electroretinographic response did not correlate with the degree of pigmentation, suggesting that other factors influenced the amount of pigmentation in these patients. (5 figures, 12 tables, 37 references)—David Shoch

The efficacy of conjunctival biopsy as a screening technique in lysosomal storage disorders. Mazow, M. L. (Houston Eye Assoc., 2855 Gramercy, Houston, TX 77025). Trans. Am. Ophthalmol. Soc. 85:471, 1987.

The term lysosomal storage disease has been used to define a group of inborn diseases of metabolism in which various cellular or extracellular constituents are stored in the lysosomes. In some cases the deficient enzyme can be defined by studying the stored material. In order to evaluate the usefulness of conjunctival biopsy in determining the type of storage material present, the author examined 83 patients. Lysosomal storage disease was ultimately diagnosed in 17. In 12 of these 17 patients (71%), a correct diagnosis was made by conjunctival biopsy. The author speculated that the accuracy of diagnosis would increase if a second biopsy specimen were obtained. However, one cannot make a definitive subclass diagnosis by conjunctival biopsy. The advantage of conjunctival biopsy is that the tissue is easily available, although the best diagnostic tool at this time remains the tissue enzyme assay. (5 figures, 9 tables, 66 references)—David Shoch

Retinal photic injury in normal and scorbutic monkeys. Tso, M. O. M. (1855 W. Taylor St., Chicago, IL 60612). Trans. Am. Ophthalmol. Soc. 85:498, 1987.

High-intensity light may damage the retina, probably by releasing free radicals and single oxygen atoms in the tissue. Ascorbic acid is active in reduction-oxidation reactions and may protect tissues against the ill-effects of free radicals. There is a high concentration of ascorbic acid in ocular tissues. The author therefore postulated that ascorbic acid might protect the eye against photic injury. He produced photic injuries in both eyes of seven monkeys fed a vitamin C-deficient diet and in both eyes of four monkeys fed vitamin C-enriched diets. He found that the retinas of the scorbutic animals showed more severe tissue damage and more retinal degeneration than the retinas of normal animals exposed to the same amount of light energy. The author suggested that retinal ascorbic acid scavenges superoxide radicals and hydroxyl radicals and reduces hydrogen peroxide. (27 figures, 3 tables, 132 references) —David Shoch

Characterization of the choroidal mast cell. Godfrey, W. A. (Dept. Ophthalmol., Kansas Univ. Med. Ctr., Kansas City, KS 66103). Trans. Am. Ophthalmol. Soc. 85:557, 1987.

Choroiditis is occasionally caused by invading organisms but more often is the result of an immunologic reaction. One of the cells often involved with such reactions is the mast cell, which is believed to be responsible for the anaphylactic reaction termed immediate hypersensitivity. The author found that mast cells were present in the rat choroid in substantial numbers. Although individuals varied, most of the mast cells were in the posterior choroid. They tended to congregate along the arterial vessels and gradually decreased in number with age. Choroidal mast cells act much like connective tissue mast cells and are present in sufficient numbers to be active in the inflammatory responses of the choroid. (19 figures, 10 tables, 86 references)—David Shoch

In vitro model of retinal photoreceptor differentiation. Lahav, M. (Dept. Ophthalmol., New England Med. Ctr., 171 Harrison Ave., Box 310, Boston, MA 02111). Trans. Am. Ophthalmol. Soc. 85:600, 1987.

The author excised the eyes of 7-day-old chick embryos and with washing and centi-

fugation made preparations of dissociated embryonic cells on a flat surface. Over several days of development, there was aggregation of retinal cells and photoreceptor differentiation. He also demonstrated beta-adrenergic receptors on developing photoreceptors by histofluorescent techniques. By transmission electron microscopy in the 12-day-old chick embryo rosettes of photoreceptors were identified as well as individual photoreceptors. These cells were attached by zonulae adherens. The nuclei had a margination of chromatin. Membranous material extended into the lumen of each rosette, resembling abortive outer segment development. (14 figures, 162 references)—David Shoch

Correction

In the article, "Pathogenesis and Therapy of Traction Detachment in Various Retinal Vascular Diseases" (Am. J. Ophthalmol. 105:170, February 1988), by Robert Machemer and John M. Williams, Sr., because of an editorial error, all measurements in nanometers were overstated by a factor of two decimal points; for example, 1,000 nm = 10 nm.

NEWS ITEMS

Send News Items to
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The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length. Announcements of meetings and courses must be received at least four months before the event.

XXVI International Congress of Ophthalmology

The XXVI International Congress of Ophthalmology is scheduled for March 18–24, 1990, in Singapore. Arthur S. M. Lim, Singapore, is President of the Congress. For further information, write The Congress Secretariat, XXVI International Congress of Ophthalmology, c/o Department of Ophthalmology, National University Hospital, Lower Kent Ridge Rd., Singapore 0511.

International Society for Optical Engineering: Laser Imaging and Photoeffects in Ophthalmology

The International Society for Optical Engineering will hold a symposium, Medical Applications of Lasers and Optics, Jan. 15–20, 1989, in Los Angeles, California. Abstracts for papers should be submitted by July 11, 1988, and the due date for manuscripts is Dec. 19, 1988. For further information write, SPIE Technical Program Committee: OE/LASE '89 Medicine, P.O. Box 10, Bellingham, WA 98227.

American Society of Ophthalmic Registered Nurses: Twelfth Annual Meeting

The American Society of Ophthalmic Registered Nurses will hold its Twelfth Annual Meeting, Oct. 8–11, 1988, in Las Vegas, Nevada. For further information, write Sue Brown, Administrator, American Society of Ophthalmic Registered Nurses, P.O. Box 3030, San Francisco, CA 94119.

Sixteenth Annual Congress of the Society of Ophthalmology: German Democratic Republic

The Sixteenth Annual Congress of the Society of Ophthalmology of the German Democratic Republic will be held April 23–28, 1990, in Rostock, West Germany. For further information, write The Congress Secretariat, XVI International Congress 1990, Eye Clinic of the Wilhelm-Pieck-University, Doberanerstr. 140, 2400 Rostock, West Germany.

American College of Veterinary Ophthalmogists: Annual Meeting

The annual meeting of the American College of Veterinary Ophthalmologists will be held Oct. 6–8, 1988, in Las Vegas, Nevada. For further information, write Thomas J. Kern, D.V.M., ACVO Program Chairman, 420 Veterinary Research Tower, New York State College of Veterinary Medicine, Cornell University, Ithaca, NY 14853.

The Christ Hospital: Update on Retina-Related Diseases and Surgery

The Christ Hospital will sponsor a course, Update on Retina-Related Diseases and Surgery: Clinically Oriented Problems and Solutions, Sept. 10, 1988, in Cincinnati, Ohio. For further information, write The Christ Hospital, Educational Services Department, 2139 Auburn Ave., Cincinnati, OH 45219.

Bascom Palmer Eye Institute: Diagnostic Ophthalmic Ultrasound: Intraocular Disease

The Bascom Palmer Eye Institute will present a course, Diagnostic Ophthalmic Ultrasound: Intraocular Disease, Nov. 3–5, 1988, in Miami, Florida. For further information, write Gaby Kressly, Bascom Palmer Eye Institute, P.O. Box 610326, Miami, FL 33261.

Manhattan Eye, Ear and Throat Hospital: Aesthetic Oculoplastic Surgery: Current Concepts

Manhattan Eye, Ear and Throat Hospital will hold a course, Aesthetic Oculoplastic Surgery: Current Concepts, Nov. 3–5, 1988, in New York, New York. For further information, write Francine Leinhardt, Course Coordinator, Manhattan Eye, Ear and Throat Hospital, 210 E. 64th St., New York, NY 10021.

Michigan Ophthalmological Society: Twentieth Annual Summer Conference

The Michigan Ophthalmological Society will hold its Twentieth Annual Summer Conference, July 21–24, 1988, on Mackinac Island, Michigan. For further information, write Christine A. Jourdain, Michigan Ophthalmo-

logical Society, 412 Eastland Professional Bldg., Harper Woods, MI 48225.

University of California, Davis: Glaucoma Course, Under Pressure II

The Department of Ophthalmology of the University of California, Davis, is sponsoring its second annual Glaucoma Course, Under Pressure II, Aug. 28–31, 1988, in Incline Village, Nevada. For further information, write Richard A. Lewis, M.D., Department of Ophthalmology, University of California, Davis, 1603 Alhambra Blvd., Sacramento, CA 95816.

University of Southern California: Pediatric Ophthalmology Cruise Seminar

The University of Southern California will hold a Pediatric Ophthalmology Cruise Seminar, Pediatric Ophthalmology and Adult Strabismus, Jan. 14–21, 1989. For further information, write Kenneth W. Wright, M.D., Childrens Hospital of Los Angeles, Division of Ophthalmology, 4650 Sunset Blvd., Los Angeles, CA 90027.

University of Toronto: International Glaucoma Review

The University of Toronto will hold an International Glaucoma Review, Sept. 23 and 24, 1988, in Toronto, Canada. For further information, write Graham E. Trope, M.D., Glaucoma Division, Department of Ophthalmology, Toronto General Hospital, 5th Floor, Eaton Wing, Ste. 306, 200 Elizabeth St., Toronto, Ontario M5G 2C4 Canada.

Personals

Bartly J. Mondino

Bartly J. Mondino was appointed Wasserman Professor of Ophthalmology at the Jules Stein Eye Institute, UCLA School of Medicine.

Myron Yanoff

Myron Yanoff has been appointed professor and chairman, Department of Ophthalmology, Hahnemann University, Philadelphia, Pennsylvania.

AMERICAN JOURNAL OF OPHTHALMOLOGY®

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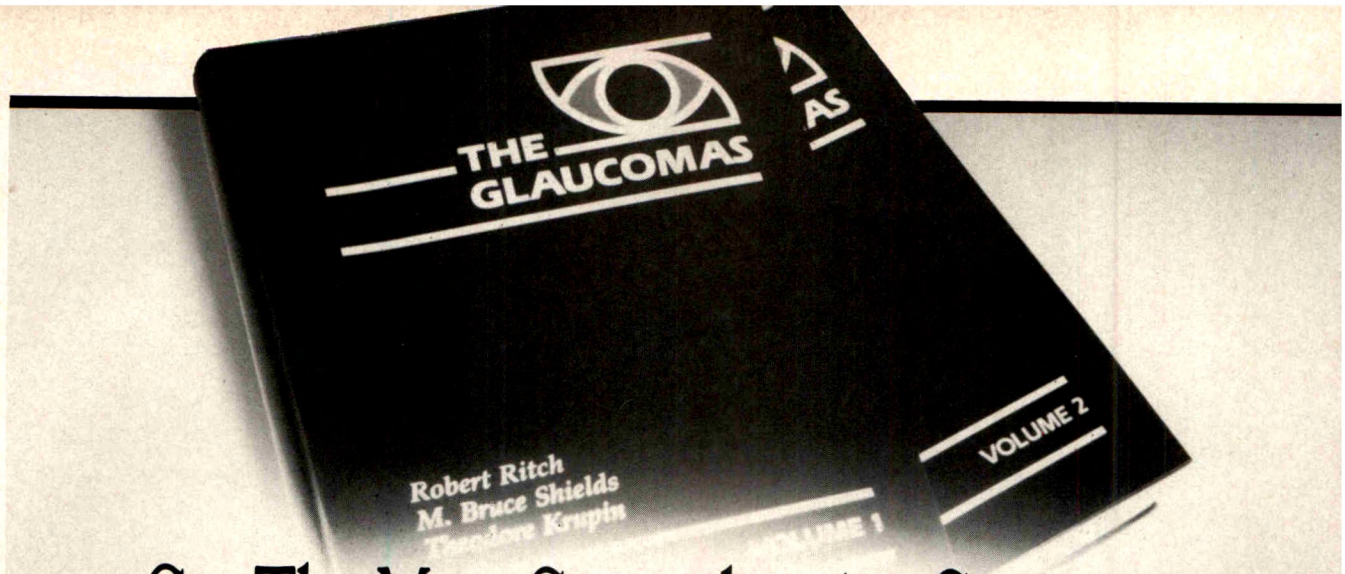
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The Effect of Radial Keratotomy on Contrast Sensitivity

M. M. Krasnov, M.A.Sc., S. E. Avetisov, N. V. Makashova, and V. R. Mamikonian

In the period after surgical correction of myopia and astigmatism in 30 patients (44 eyes) by radial keratotomy, contrast sensitivity deteriorated slightly. The disturbances, however, were transitory, and the general trend was toward restoration of function. Strict adherence to an adequate operative technique prevented a marked decline in contrast sensitivity. The decrease must be considered before surgery, particularly in patients who need a high degree of fine motor control.

© American Journal of Ophthalmology 105:651–654, June, 1988

Necrotizing Keratitis Caused by *Capnocytophaga ochracea*

David G. Heidemann, M.D., Stephen C. Pflugfelder, M.D., Jan Kronish, M.D., Eduardo C. Alfonso, M.D., Steven P. Dunn, M.D., and Saul Ullman, M.D.

We studied three cases of *Capnocytophaga* keratitis that demonstrated stromal necrosis and a ring infiltrate. In all cases, the keratitis occurred in a previously diseased or traumatized cornea. One patient was treated with chronic antiamoebic therapy for presumed *Acanthamoeba* keratitis. Two cases resulted in corneal perforation. Laboratory isolation was difficult because of slow, fastidious growth. *Capnocytophaga* is not uniformly sensitive to commonly used topical antibiotics such as the cephalosporins and aminoglycosides, but may respond to treatment with topical clindamycin.

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Mycobacterium fortuitum Keratitis

Pravin U. Dugel, M.D., Gary N. Holland, M.D., Harry H. Brown, M.D., Thomas H. Pettit, M.D., John D. Hofbauer, M.D., Kenneth B. Simons, M.D., Henry Ullman, M.D., Patricia E. Bath, M.D., and Robert Y. Foos, M.D.

Two of four cases of *Mycobacterium fortuitum* keratitis occurred after corneal surgery with contact lens wear, one was associated with extended contact lens wear alone, and one occurred after a foreign body injury. All cases were characterized by pain, conjunctival hyperemia, stromal inflammation, and ulceration. Diagnosis was made by culture and acid-fast staining of corneal scrapings. On the basis of published experience with amikacin for the treatment of nonocular *M. fortuitum* infections, three patients were treated with topical amikacin. Two patients responded clinically, but histopathologic examination of a penetrating keratoplasty specimen in one of the two disclosed persistent infection. One patient was cured of early disease by debridement alone. Rapid diagnosis and absence of corticosteroid use were the two most important determinants of successful therapy. In advanced cases, infection may be cured and useful vision restored by penetrating keratoplasty.

© American Journal of Ophthalmology 105:661–669, June, 1988

Toxic Endothelial Degeneration in Ocular Surface Disease Treated With Topical Medications Containing Benzalkonium Chloride

Michael A. Lemp, M.D., and Lorenz E. Zimmerman, M.D.

We examined a 56-year-old man with keratoconjunctivitis sicca and marked ocular surface disease in whom the prolonged frequent use of topical medications containing the preservative benzalkonium chloride was associated with corneal endothelial damage requiring corneal transplantation in one eye. The histopathologic findings on examination of the excised button were consistent with toxic endothelial disease. Postoperatively, the patient's symptoms continued until the preservative-containing medications were substituted with nonpreserved saline eyedrops.

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Use of an Angiotensin Converting Enzyme Inhibitor in Ocular Hypertension and Primary Open-Angle Glaucoma

William H. Constad, M.D., Philip Fiore, M.D., Cesar Samson, M.D., and Alfonse A. Cinotti, M.D.

We studied the effects of a new topical angiotensin converting enzyme inhibitor, SCH 33861, in lowering intraocular pressure in 20 patients with ocular hypertension or primary open-angle glaucoma. In a double-masked, four-way crossover study with placebo and timolol, SCH 33861 was well tolerated and effective in lowering intraocular pressure. The magnitude of the drug's effect in lowering intraocular pressure was less than that of timolol 0.5%.

© American Journal of Ophthalmology 105:674–677, June, 1988

Comparison of Intraocular Pressure Measurements With the Oculab Tono-Pen vs Manometry in Humans Shortly After Death

Volker Hessemer, M.D., Ralf Rössler, and Karl W. Jacobi, M.D.

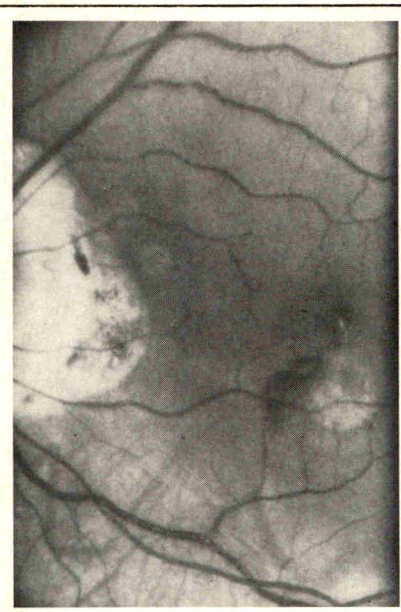
We compared the Oculab Tono-Pen, a miniaturized Mackay-Marg tonometer, with a Statham membrane manometer in six humans (12 eyes), three to six hours after death. The intraocular pressure was changed in 5- to 10-mm Hg steps in a range between 0 and 60 mm Hg by an infusion system. The correlation coefficient of the relation of Tono-Pen readings vs manometrically determined intraocular pressures was .99. Compared to the manometer, the Tono-Pen gave a small underestimation of intraocular pressure above 17 mm Hg or overestimation below 17 mm Hg. The maximal deviation of the Tono-Pen readings from the manometer readings was 2.5 mm Hg. In our experience the correspondence between Tono-Pen and manometer readings was superior to the correspondence between the readings obtained with the original Mackay-Marg tonometer and manometry.

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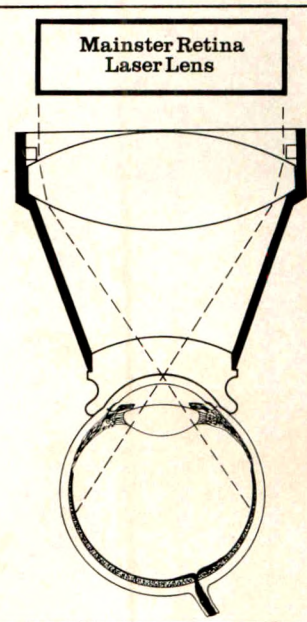


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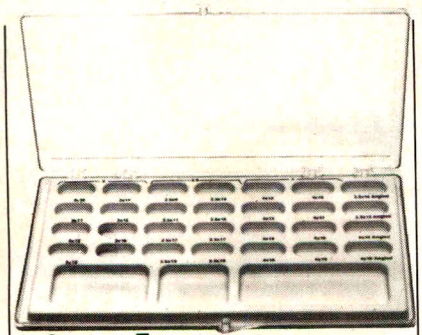
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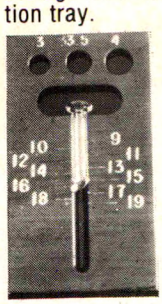
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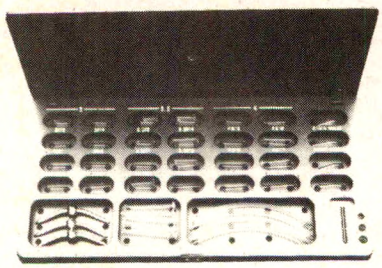
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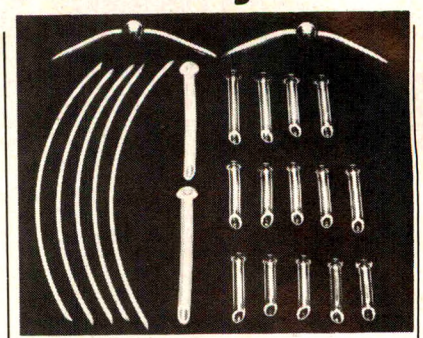
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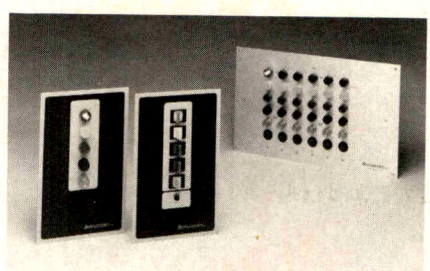
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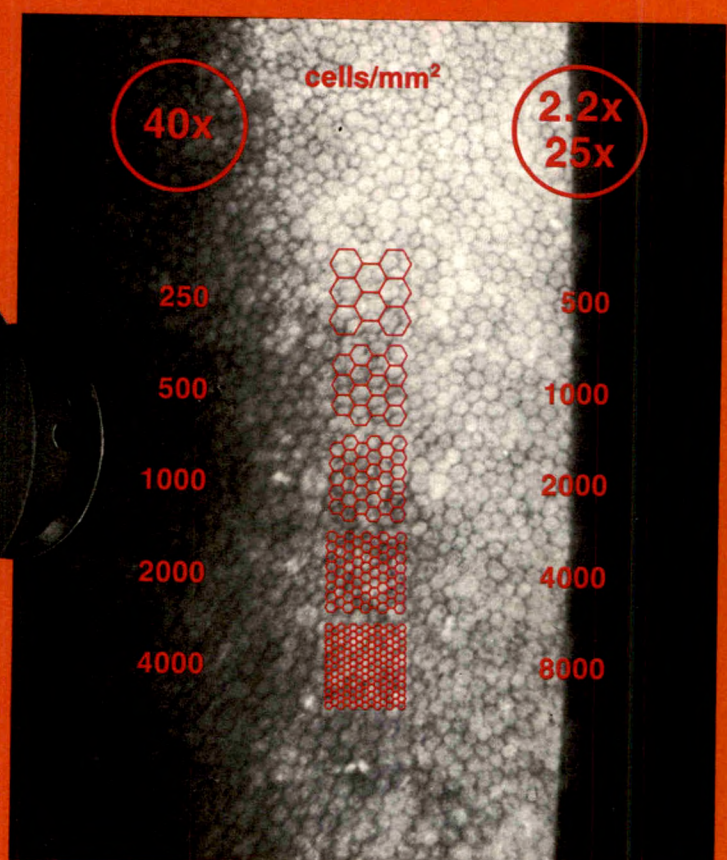
3. Name (*print*): _____ Signature: _____ Date: _____

   Home Address: _____

4. Name (*print*): _____ Signature: _____ Date: _____

   Home Address: _____

Cells by the thousand —— up to 9 mm² with the Haag-Streit Endo-set.







Endo- set

The **Eisner** contact glass, which is the heart of the Endo-set, provides wide field biomicroscopic observation of the endothelium of the cornea in specular reflection and slit lamp photography of these cells. The **Eisner** lens gives 2.2x magnification, free from spherical aberration, coma and astigmatism.

A specially designed 25x eyepiece with a **McIntyre** comparison grid allows estimation of the endothelium cell density with and without contact glass.

The Endo-set, consisting of 1 **Eisner** lens and 1 eyepiece 25x with **McIntyre** comparison grid offers significant advantages in examination procedures.

For full details on this advanced method of examining endothelium cells, contact us or your nearest HAAG-STREIT distributor.

HAAG-STREIT

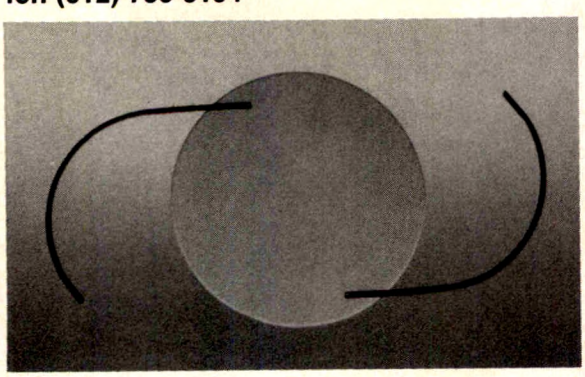
Haag-Streit Service Inc.
Subsidiary of Haag-Streit AG.,
Berne, Switzerland
7 Industrial Park,
Waldwick, New Jersey 07463
(201) 445-1110

NEW PRODUCTS AND SERVICES

New products and services considered by the editors to be of interest to our readers are described on the basis of information supplied by the companies cited. Publication of these notices does not imply endorsement or warranty by The Ophthalmic Publishing Company, publishers of The American Journal of Ophthalmology, for these products and services.

Intraocular Lenses

3M Vision Care
Dept. VC88-01
P.O. Box 33600
St. Paul, MN 55133-3600
Tel: (612) 736-3194

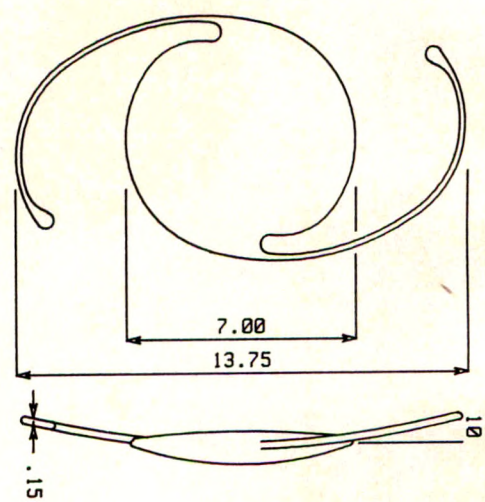


A new posterior chamber intraocular lens featuring a 7-mm optical zone with no ridges and a no-holes option, has been introduced by 3M Vision Care. The Style 12LE modified C-loop lens, indicated for surgical correction of aphakia following extracapsular cataract extraction, minimizes the potential for edge glare from intraocular lenses in patients with asymmetric or dilated pupils. The 7-mm meniscus optic maximizes the usable optical area by eliminating ridges that can cause glare. The no-holes option eliminates another potential source of glare.

The optic, made of ultraviolet-absorbing PMMA, has a smooth, rounded edge. The meniscus optic is designed to facilitate laser capsulotomy. Polypropylene open-loop haptics offer a flexible, broad arc of fixation to minimize stress on delicate tissues.

This lens is available in powers ranging from 25.0 to 14.5 diopters in 0.5-diopter increments and from 14.0 to 9.0 diopters in 1.0-diopter increments. Optics are available with zero or two positioning holes (0.3 mm).

Storz Ophthalmics, Inc.
1365 Hamlet Ave.
Clearwater, FL 34616
Tel: (800) 237-5906 (National)
(800) 282-1208 (Florida)



A full 7-mm optic zone and short C haptics that mimic the flexibility of Prolene loops and that of three-piece PMMA designs are featured in a new Coburn one-piece intraocular lens. Introduced by Storz Ophthalmics, Inc., the Coburn Model 95-UV one-piece PMMA posterior chamber intraocular lens combines these design traits with its biconvex optic and Smooth-Flex finishing process.

For placement in the capsule or ciliary sulcus, the Model 95-UV combines stability with ease of insertion. The arch of fixation provided by the step-vaulted, modified C loop configuration is designed to distribute evenly the force to the capsule to promote and maintain centration.

The Coburn Model 95-UV is available in dioptric powers ranging from +8 to +30 in 0.5-diopter increments.

THE DRY EYE SPECIALISTS

EAGLE VISION-FREEMAN™ PUNCTUM PLUG KIT

Patent # 3,949,750,750

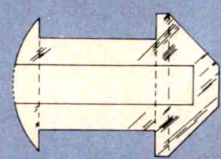
For use in the treatment of keratitis sicca by reversible occlusion of the punctum and canaliculus.

Introducing

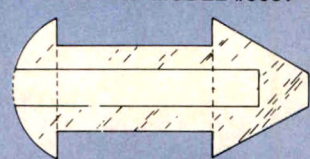
THE *NEW* SHORT PLUG WITH REDUCED DOME CONFIGURATION

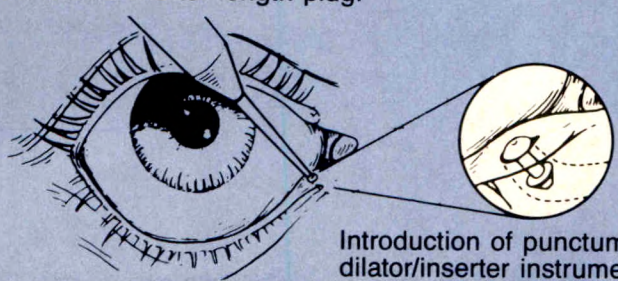
In response to physicians who have requested a smaller dome and shorter length plug.

NEW MODEL #0003



STANDARD MODEL #0001





Introduction of punctum plug held in place by inserter end of dilator/inserter instrument.

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Lactoferrin Immunological Test System

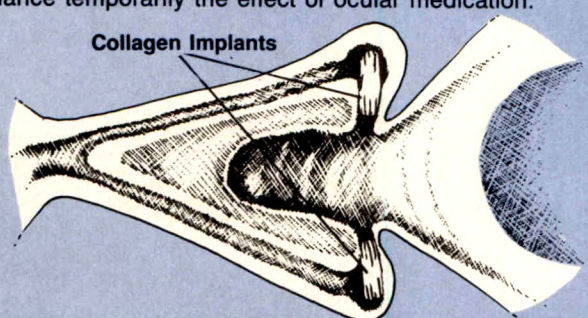
Use when Schirmer values are questionable.

The first new approved method for clinical assessment of lacrimal gland function. Simple and quick in-office procedure.



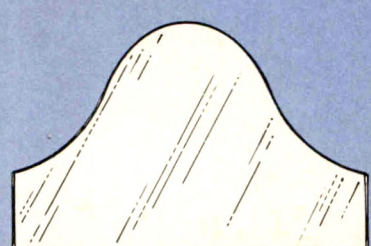
Temporary Intracanalicular Collagen Insert

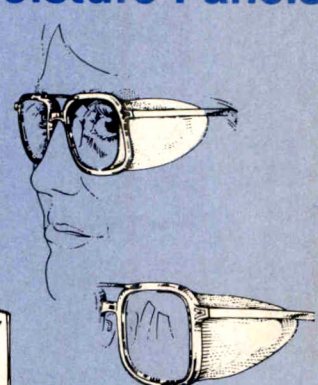
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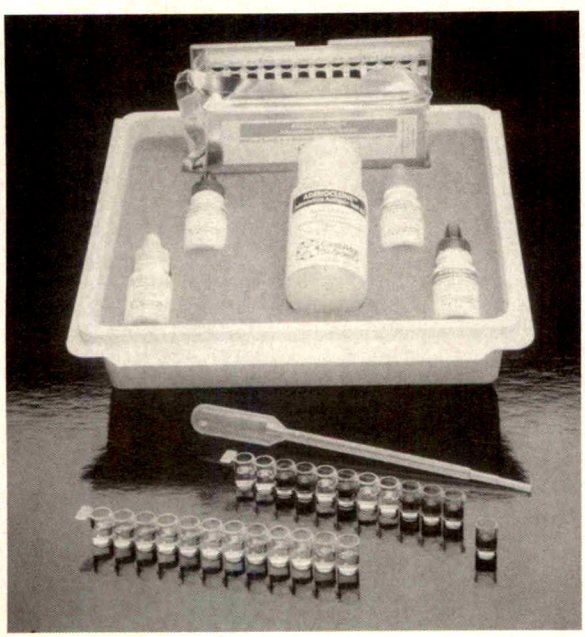
6485 POPLAR AVE., MEMPHIS, TN 38119

1-800-238-7584 IN TN 901-767-3937

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Diagnostic Devices

Cambridge BioScience Corp.
365 Plantation St.
Worcester, MA 01605-9979
Tel: (617) 797-5777

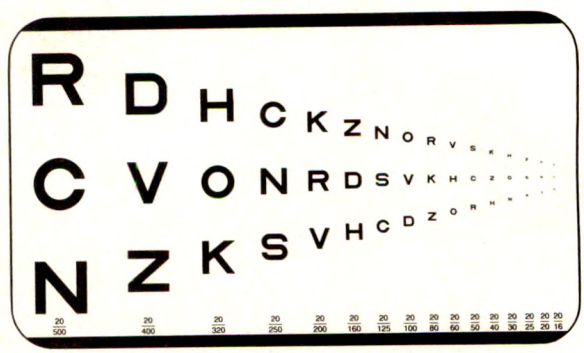


Cambridge BioScience Corporation has received Food and Drug Administration clearance to market an in vitro diagnostic test kit for the detection of human adenovirus. Available for immediate delivery, Adenoclone-EIA is an immunoassay kit for the rapid detection of adenovirus in stool samples and cell culture isolates from ophthalmic, respiratory, and enteric specimens. It uses a monoclonal antibody directed against the group-specific antigen and can detect all known human adenoviruses.

Adenoclone-EIA, available in a 48 test kit, is a 75-minute procedure that requires no reagent preparation or pipettes. All reagents are supplied in convenient, ready-to-use, color-coded dropper bottles. Breakaway wells accommodate single or batch testing. No incubation or special laboratory instrumentation is needed to run the assay as all incubations are carried out at room temperature and the test can be read visually. There is no equivocal or gray zone; the results are either positive or negative.

Clinical studies show 99% sensitivity and 100% specificity as compared with cell culture confirmation or direct stool specimen testing.

Focus Ophthalmics
P.O. Box 7451
Westchester, IL 60153
Tel: (312) 450-6066



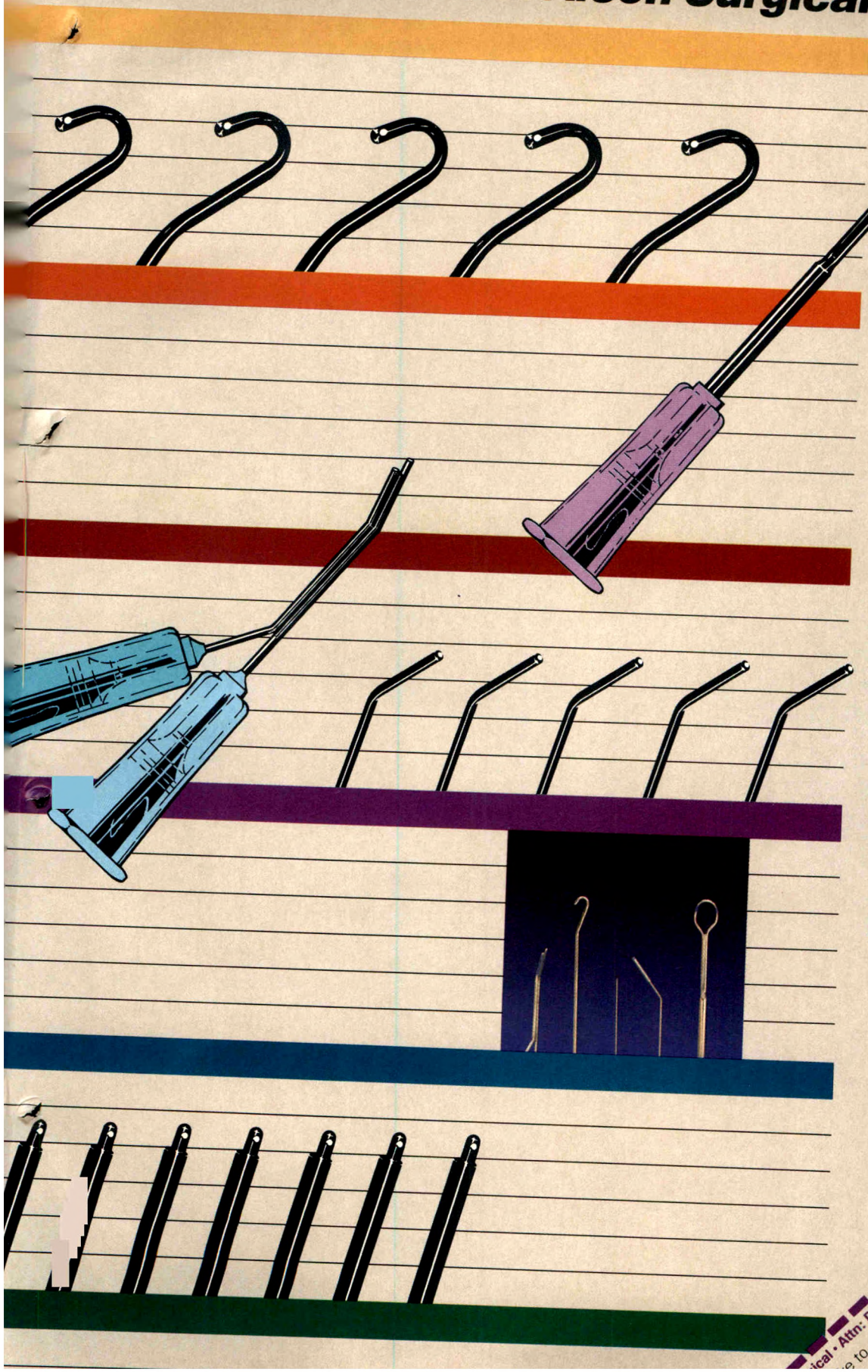
A new near vision card which allows rapid and accurate assessment of visual acuity in even the most difficult of circumstances has been designed. Initial research and development of the card took place in the department of ophthalmology at the Cook County Hospital, Chicago. The card takes advantage of the normal reading tendency, left to right. The face of the card is composed of Sloan letters 20/500 to 20/16 in size increments of 1/10 log units as adopted by the ETDRS group. The reverse of the card has the same sequence of letters allowing the examiner to read along with the patient. The back also contains Snellen distance equivalents in feet and meters, Jaeger type, printer's points, logMAR, and Snellen M units. A millimeter rule and pupil gauge are also included. This new card will enable examiners to assess visual acuity quickly and accurately at the bedside and in other less than ideal circumstances. The cards are currently available in cardboard and will soon be produced in high-quality matte plastic.

Surgical Devices

Western Medical Products, Inc.
11211 Sorrento Valley Rd., Ste. X
San Diego, CA 92121
Tel: (609) 546-0608

Western Medical Products has introduced a reuseable/disposable zirconia ceramic knife blade. The blade, which is good for 30 uses, may be sterilized by any approved method. The Lancet 1 and 2 mm, 30-degree, and Tooke blades are available for $35.00 each; 3- and 3.5-mm blades are also available.

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Contact Lens Supplies

Barnes-Hind, Inc.
810 Kifer Rd.
Sunnyvale, CA 94086
Tel: (800) 854-2790 (National)
(800) 542-6000 (California)

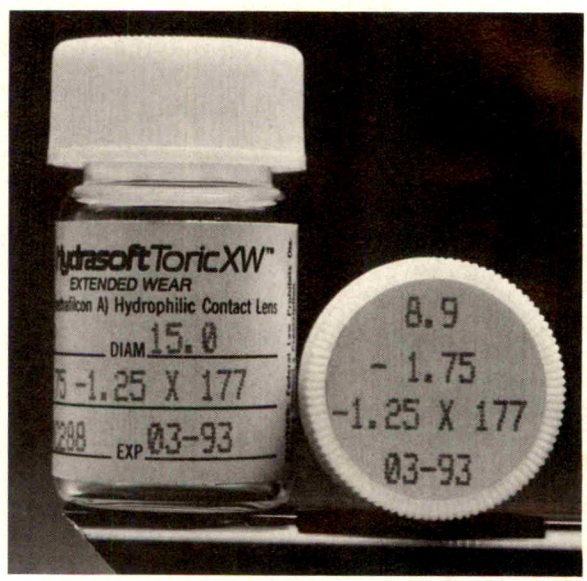


Consept, an advance in contact lens care, was announced by Sola Barnes-Hind, a Pilkington Visioncare Company. The Soft Mate Consept System includes Consept-1, a combined one-step lens cleaning and hydrogen peroxide disinfecting solution, and Consept-2, a preservative-free multidose neutralizer in an aerosol spray delivery system.

The Soft Mate Consept System combines both surfactant daily lens cleaning and hydrogen peroxide disinfection of lenses simultaneously in one ten-minute step in the Consept-1 Solution. After one-step cleaning and disinfection in Consept-1, lenses are rinsed and neutralized in Consept-2 preservative-free rinsing and neutralizing aerosol spray for ten minutes. Consept-2 is preservative-free for sensitive eyes and pH balanced to human tears for comfort.

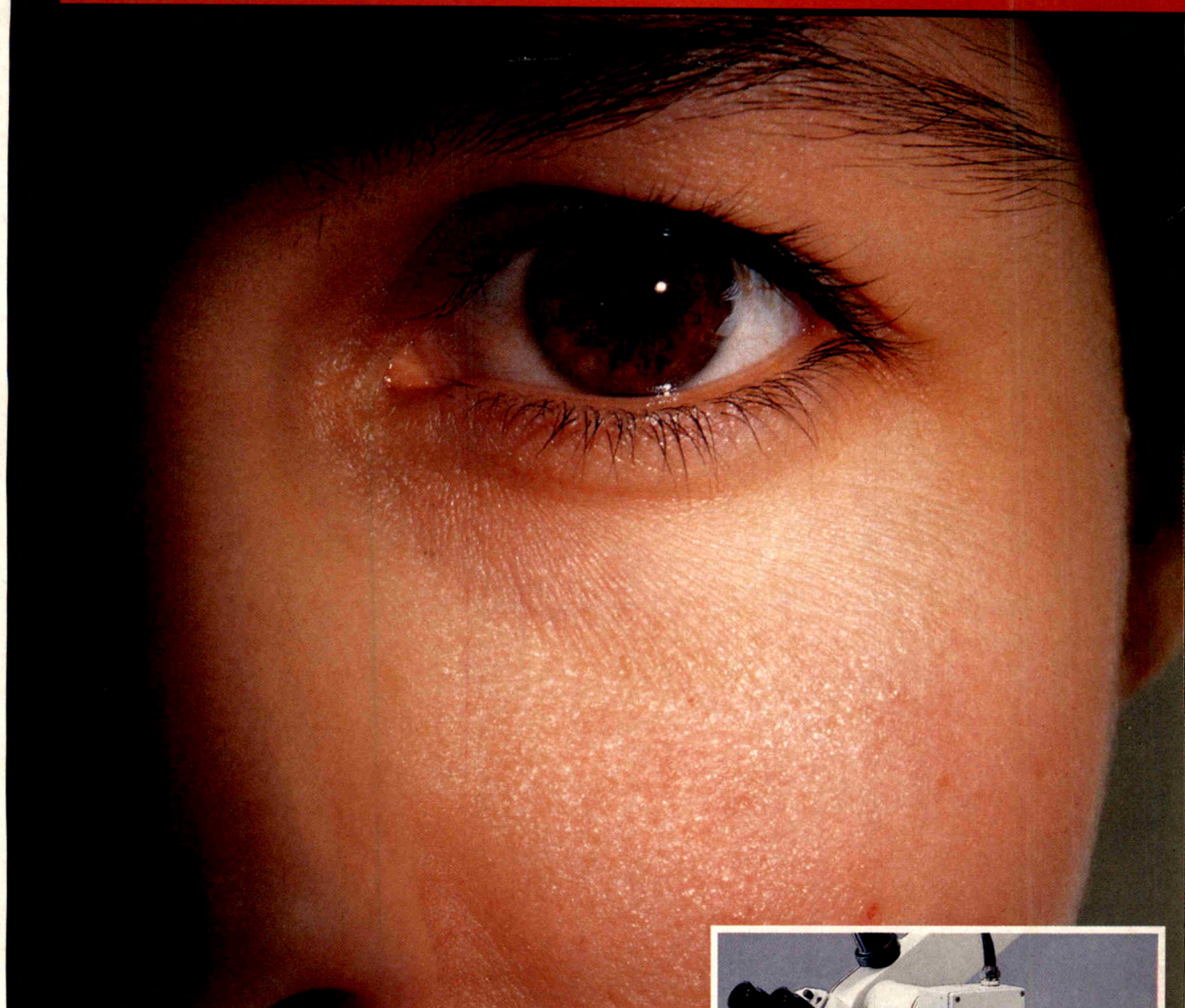
Contact Lenses

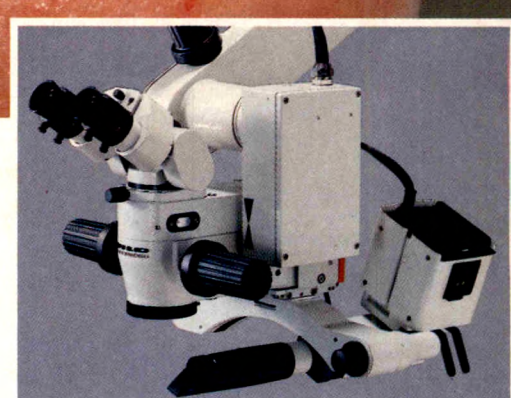
CoastVision
18368 Enterprise Lane
Huntington Beach, CA 92648
Tel: (800) 341-2020 (National)
(714) 841-3302 (California)



CoastVision has introduced the Hydrasoft Toric XW, a 55% water (methafilcon A) flexible-wear contact lens, approved for one to seven days of wear. The Hydrasoft Toric XW is the only flexible-wear soft toric approved with a cylinder range over −2.50 diopters. Spherical powers will be available from +6.00 to −12.00 diopters and cylinder power to −5.00 diopters in any axis. The Hydrasoft Toric XW is an ultrathin version of the Hydrasoft daily-wear toric. The new toric lens has an 8.9-mm base curve, 15.0-mm diameter, and is a back surface toric with 1.0 diopter of prism ballast with eccentric lenticulation. Like the daily-wear Hydrasoft Toric, the flexible-wear Hydrasoft Toric XW is a stable and comfortable lens.

TO SEE OR NOT TO SEE





For patient and surgeon alike, the unique illumination design of Wild M600 series surgical microscopes offers ideal conditions for microsurgery of the eye, because:

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GENERAL OPHTHALMOLOGIST: Growing four-physician practice in southeast Virginia is seeking a general ophthalmologist with subspecialty preferred but not necessary. Send C.V. to Medical & Surgical Eye Specialists, Inc., 801 Medical Tower, Norfolk, Virginia 23507.

GENERAL OPHTHALMOLOGIST

To join expanding eye department at the multispecialty Kaiser Permanente Medical Center, a prepaid HMO, at Oakland, CA. Competitive salary and generous benefit package offered. The eye department consists of 10 M.D.'s with subspecialties in glaucoma, pediatrics, oculoplastics and retina, and 10 O.D.'s. Fully equipped offices with excellent technician support. Send C.V. to Richard A. Brown, M.D., 280 W. MacArthur Blvd., Oakland, CA 94611.

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ASSOCIATE: Expanding prestigious general ophthalmology practice in Fresno, California seeks associate. Retinal experience and/or refractive surgery experience preferred. Resume and picture to: Practice administrator, 5359 North Fresno Street, Suite 101F, Fresno, CA 93710.

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PLASTICS

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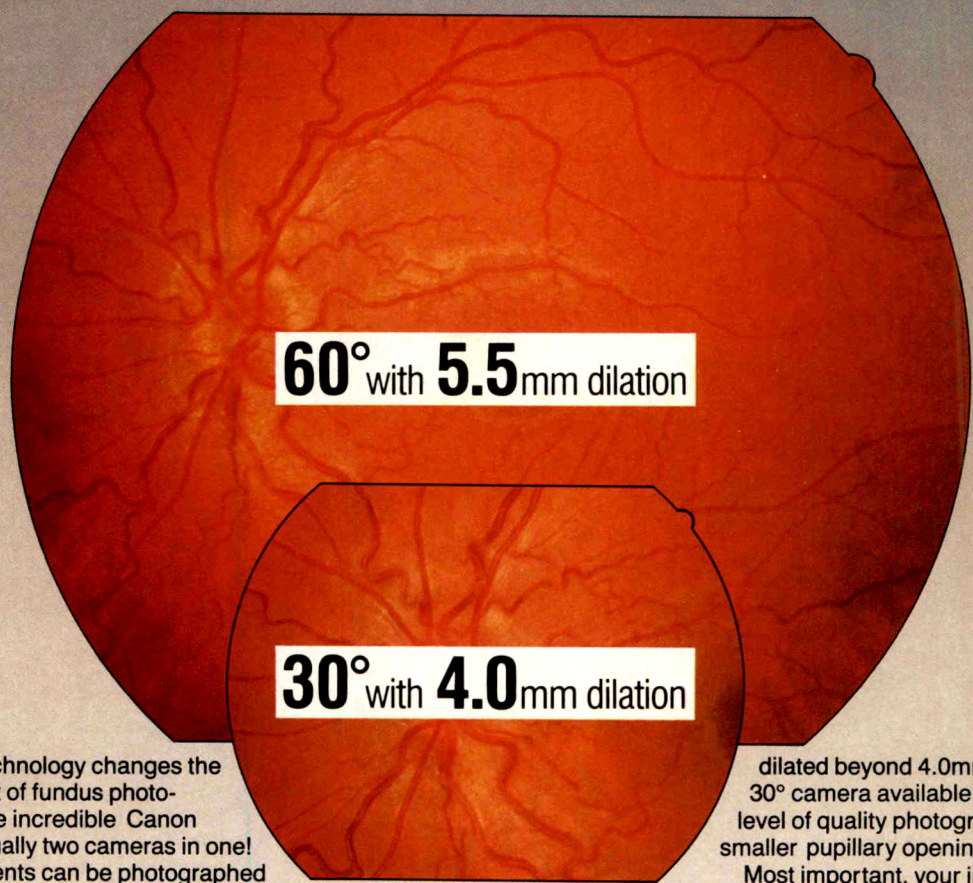
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Wanted to join an outstanding and busy subspecialty ophthalmic group in the Southeast. Experience required. Excellent income and vacation schedule. Benefits include diversified insurance program, continuing education, automobile and retirement program. Our practice utiliizes college-trained ophthalmic technicians and registered nurses, thereby enabling the new physician to actively practice the medical aspects of ophthalmology. William J. Collis, M.D., 2134 Nicholasville Road, Suite 3, Lexington, Kentucky 40503.

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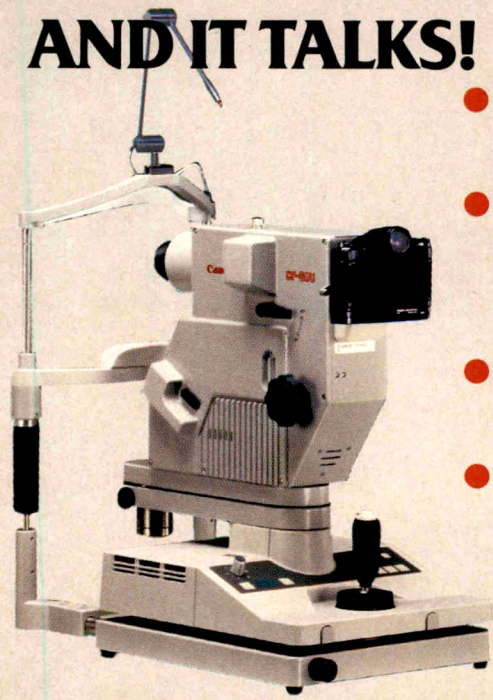
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V.A. LaFleur, M.D.
Associate Medical Director
Colorado Permanente Medical Group, P.C.
2045 Franklin Street
Denver, CO 80205
(303) 861-3262

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Carol R. Kollarits, M.D.
Medical Director
Eye Institute of Northwestern Ohio
5555 Airport Highway, Suite 110
Toledo, Ohio 43615

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